Coexistence of cardiac amyloidosis with coronary artery disease and the challenges in medical management

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BACKGROUND

Advances in multimodality cardiac imaging have led to an increased identification of cardiac amyloidosis (CA), especially transthyretin amyloidosis (ATTR). Diagnosis of CA may pose several management dilemmas, especially with coexistent cardiac comorbidities. We present a challenging case of concomitant diagnoses of cardiac ATTR and ischemic heart disease, and the associated management dilemmas, along with a brief review of the currently suggested management strategies.

CASE PRESENTATION

A 69 year-old Caucasian male with diabetes mellitus, dyslipidemia, hypertension, peripheral arterial disease, and a history of stroke was admitted to the hospital with increasing typical exertional chest pain and light-headedness for the past few months. On presentation to the emergency department, his vital signs were within normal range (afebrile, heart rate 75 bpm, blood pressure 110/74 mmHg, respiratory rate 18 breaths per minute, and 97% O_2 saturation on room air) with an overall unremarkable physical examination. Laboratory data were notable for a mildly elevated troponin-I level of 0.08 ng/mL (normal < 0.06 ng/mL) and brain natriuretic peptide level of 335 pg/mL (normal < 100 pg/mL). Electrocardiogram (ECG) showed atrial fibrillation and a normal QRS voltage (Figure 1). Chest x-ray displayed minimal pulmonary vascular congestion.

The patient was referred for a coronary angiogram that revealed significant triple vessel coronary artery disease (CAD) including severe stenosis in the proximal-mid left anterior descending artery, moderate stenosis in the mid left circumflex artery, and severe stenosis in the mid right coronary artery (Figure 2). A transthoracic echocardiogram showed global hypokinesis with severely reduce left ventricular ejection fraction of 30%, moderate concentric hypertrophy, moderately reduced right ventricular systolic function and moderate biatrial dilatation (Figure 3A). There was only mild valvular regurgitation on echocardiogram. At our institution, strain imaging is routinely performed by the sonographer if they notice moderate-to-severely increased left ventricular wall thickness. Speckle tracking echocardiography (strain imaging) analyzes motion by tracking speckles in the ultrasound image. These acoustic markers are statistically equally distributed throughout the myocardium and a special software tracks the geometric shift of each speckle during a cardiac cycle, that represents local tissue movement. Thus, the motion pattern of myocardial tissue is reflected by the motion pattern of the speckles. Strain is simply calculated as the change in length divided by the original length and expressed as a percentage. One characteristic finding in cardiac amyloidosis is an apical sparing, longitudinal strain abnormality on speckle tracking echocardiography. This sparing pattern can be quantified as follows:

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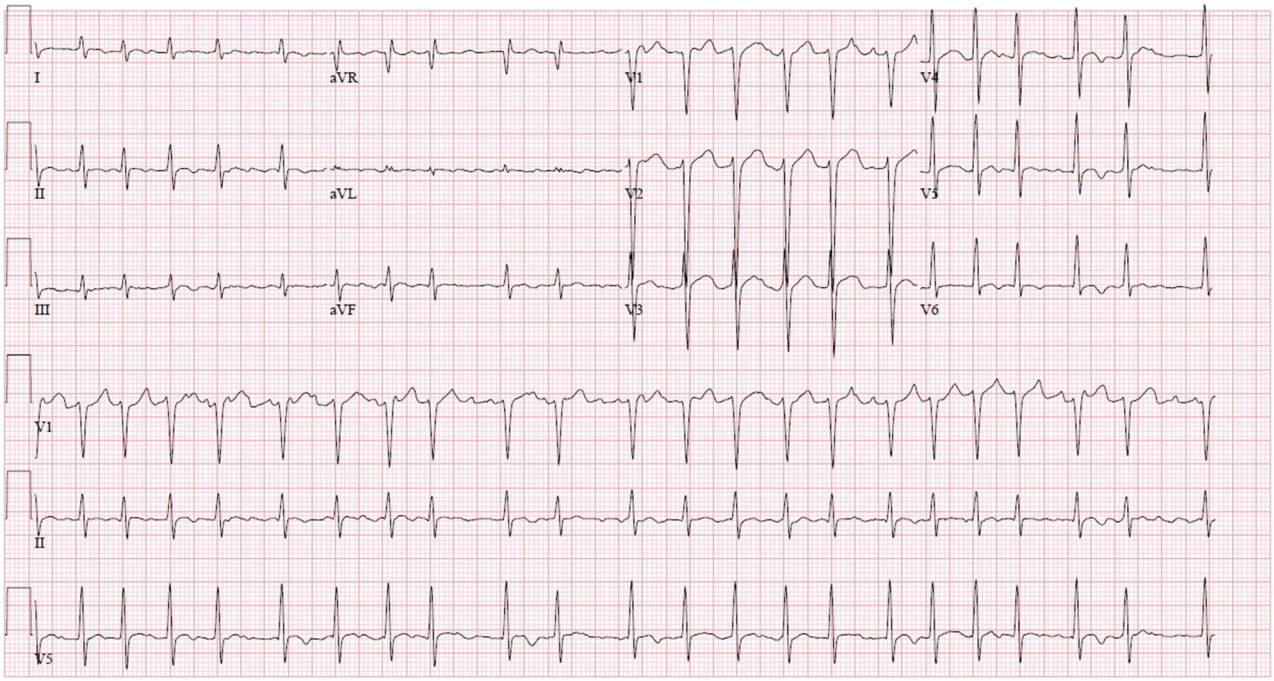

Figure 1. Electrocardiogram. Atrial fibrillation with frequent polymorphic premature ventricular contractions and a normal QRS voltage.

$$\text{(a) Apical sparing strain pattern } (ASP) = \frac{\text{Average LS in 5 apical segments}}{(\text{Average LS in 6 basal segments} + \text{Average LS in 6 mid segments})},$$

where LS is longitudinal strain. ASP pattern is said to be present when this ratio is > 1. This cutoff is based on that reported by Phelan et al. from a 18-segment LV model,[1] and essentially represents significantly better average LS in the apex compared with the sum of the average mid and basal segmental LS. In this case, strain imaging revealed an ASP ratio of 3.6 (Figure 3B). Patient was referred to cardiothoracic surgery for coronary artery bypass grafting evaluation, who requested a cardiac magnetic resonance imaging (MRI) for assessment of myocardial viability. Cardiac MRI was noteworthy for subendocardial infarction in the left anterior descending artery distribution, with preserved viability. However, cardiac MRI unexpectedly demonstrated diffuse myocardial-delayed gadolinium enhancement in the right ventricle and both atria, along with the patchy mid-myocardial enhancement of the left ventricle (Figure 4). The MRI and echocardiographic findings were highly concerning for CA.

To ascertain the diagnosis of CA, a technetium-99m pyrophosphate (Tc-99m PYP) scan was performed, along with determination of the presence of immunoglobulin light chains in the serum and urine, and serum immunofixation. Resting planar images showed diffuse prominent cardiac uptake of Tc-99m PYP, at 1 hour after injection of 21.4 mCi of Tc-99m PYP. Tomographic reconstruction of SPECT myocardial perfusion images confirmed significant myocardial uptake of the isotope, with no blood pool activity (Figure 5). Semiquantitative visual score of radioisotope uptake in the myocardium was graded as 3, and the heart-to-contralateral lung (H/CL) ratio was 1.6, at

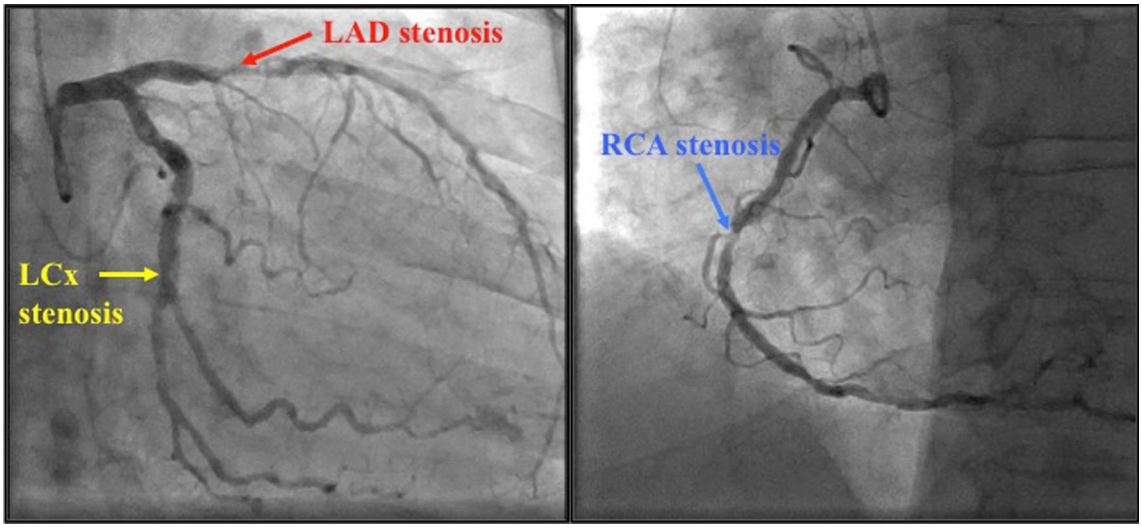

Figure 2. Coronary angiogram. Images show significant multivessel coronary artery disease, including severe stenosis in the proximal-mid left anterior descending (LAD) artery—red arrow), moderate stenosis in the mid left circumflex (LCx) artery—yellow arrow, severe stenosis in the mid right coronary artery (RCA)—blue arrow.

1 hour after tracer injection. The results of the Tc-PYP scan, along with the absence of serological evidence of abnormal light chains or monoclonal gammopathy, confirmed the diagnosis of cardiac ATTR in this patient with a new diagnosis of triple vessel CAD.

The patient underwent a successful 4-vessel bypass surgery. Guideline directed medial therapy for CAD and severe systolic LV dysfunction was instituted—including aspirin 81 mg oral daily, atorvastatin 80 mg oral daily, metoprolol tartrate 25 mg oral twice a day, and lisinopril 2.5 mg oral daily. On postoperative day 1, the

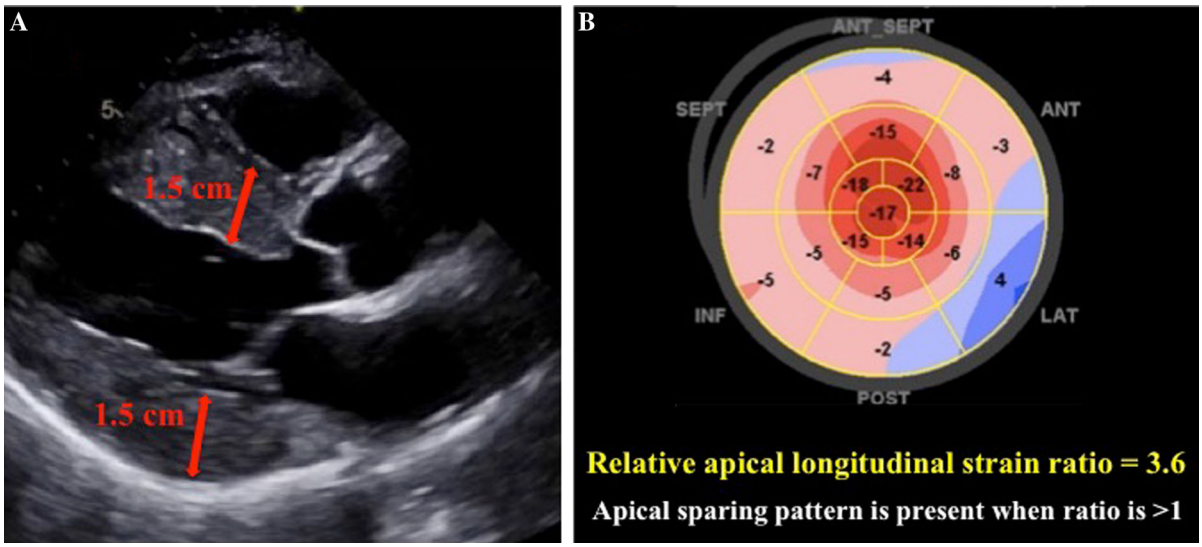

Figure 3. Transthoracic echocardiogram. **A** parasternal long axis view showing moderate concentric left ventricular hypertrophy (anteroseptal and inferolateral wall thicknesses at end-diastole of 1.5 cm each), and **B** 17-segment model of the left ventricle demonstrating apical sparing strain pattern on speckle tracking imaging. Apical sparing pattern (ASP) is calculated as a ratio of the average longitudinal strain of the 5 apical segments divided the average longitudinal strain of the 6 mid and 6 basal segments, and ASP is present when this ratio is > 1(1).

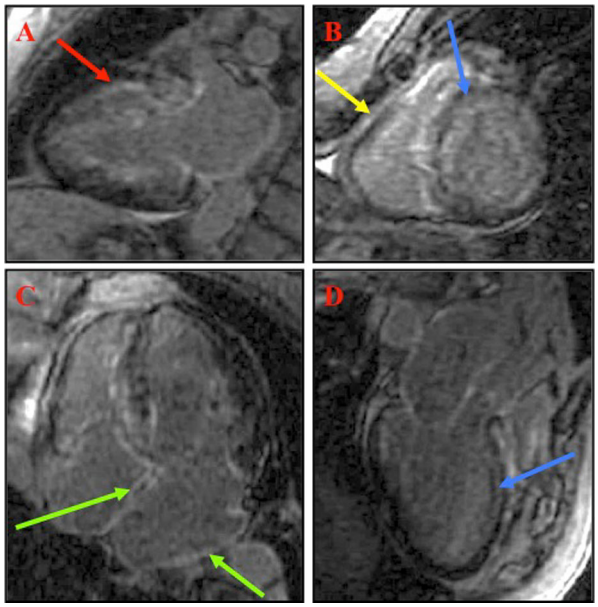

Figure 4. Cardiac magnetic resonance imaging. Cardiac MRI performed for viability assessment revealed subendocardial infarct in the left anterior descending (LAD) artery distribution (red arrow), diffuse right ventricular myocardial (yellow arrow), patchy left ventricular myocardial (blue arrows), and biatrial (green arrows) delayed gadolinium enhancement.

patient developed a rapid ventricular rate with the preexisting atrial fibrillation for which amiodarone was added. The subsequent day, he developed high-grade atrioventricular block with hemodynamic compromise that persisted despite discontinuation of amiodarone and metoprolol. The patient underwent an urgent placement of a dual chamber implantable cardioverter defibrillator (ICD) for the management of advanced heart block and for primary prevention of sudden cardiac death. He was eventually discharged on guideline directed medical therapy for severe systolic ischemic cardiomyopathy that included aspirin, high intensity statin, metoprolol succinate 50 mg oral daily, lisinopril 2.5 mg oral daily, spironolactone 25 mg oral daily, along with amiodarone and warfarin for atrial fibrillation. In the subsequent few months following his discharge, the patient had two admissions for decompensated heart failure, despite adherence to guideline-directed medical therapy and dietary recommendations, and one admission for near syncope secondary to significant orthostatic hypotension. Doses of both, beta-blocker (BB) and angiotensin converting enzyme inhibitor (ACEi) were initially reduced, with eventual discontinuation due to symptomatic hypotension, that otherwise failed to improve. Amiodarone was also discontinued as there was no ongoing need as the patient's heart rate remained well controlled despite intermittently being in paroxysmal atrial fibrillation. The patient ultimately attained hemodynamic stability and was maintained on a regimen of aspirin, statin, warfarin, and spironolactone. He was seen in the cardiomyopathy clinic after hospital discharge and remained hemodynamically stable, with NYHA class II symptoms and no evidence of decompensated systolic heart failure. He was started on doxycycline and tauroursodeoxycholic acid (TUDCA) for treatment of cardiac ATTR. Diflunisal was not initiated due to the potential risk of increased bleeding events with concomitant aspirin and warfarin therapy.

DISCUSSION

We describe a case of concomitant new diagnoses of cardiac ATTR and ischemic heart disease leading severe combined amyloid and ischemic cardiomyopathy, with conflicting medical management for both of these states. Cardiac ATTR is generally seen among older individuals, and increasing age is also associated with an increasing prevalence of CAD. It is thus intuitive that these two varied disease states are likely to coexist, although little is known on how to adequately manage them. This is particularly true when systolic dysfunction is present, as guidelines recommend medical management with beta blockers and ACEi or angiotensin receptor blockers (ARBs) for mortality benefit, which can be counterproductive and worsen survival among those with cardiac ATTR.

The diagnosis of CA maybe camouflaged by CAD, due to overlapping clinical presentation of heart failure, arrhythmias, and abnormal elevations of cardiac biomarkers. A recognized mechanism of myocardial dysfunction in amyloidosis is via intramural amyloid deposits (in ATTR) and circulating light chain related toxicity (in AL). Obstructive intramural coronary amyloidosis may lead to ischemic heart disease in the absence of epicardial coronary atherosclerosis.[2] Progressive coronary luminal obstruction by intramural amyloid deposits may lead to angina, and even myocardial infarction in the event of complete occlusion, along with progressive heart failure symptoms. Similarly, CA may also worsen preexisting coronary artery disease. Perivascular and interstitial amyloid deposition leads to increased LV mass, restrictive cardiomyopathy with high LV filling pressures, along with endothelial dysfunction and autonomic neuropathy.[3,4] These extravascular amyloid deposits may compress coronary microvasculature leading to increased coronary microvascular resistance. Augmented LV mass leads to a disproportionately reduced myocardial capillary density, in addition to decreased diastolic coronary microvascular perfusion due to higher LV filling pressure.

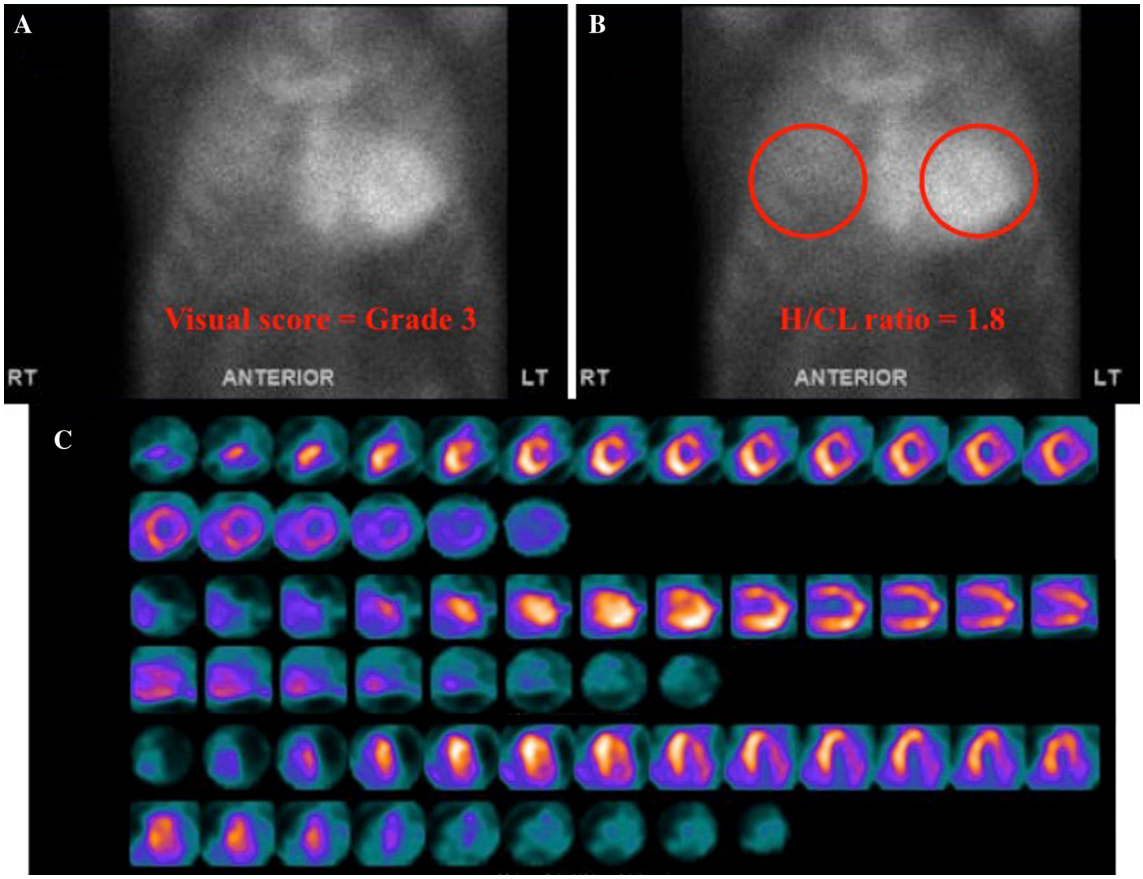

Figure 5. Positive Technetium-99m pyrophosphate (PYP) imaging. **A** Planar images showing prominent cardiac uptake of Tc-99m PYP at 1 hour after tracer injection. Semiquantitative visual score of radioisotope uptake in the myocardium is Grade 3 (myocardial uptake > rib uptake), **B** Heart-to-contralateral lung (H/CL) ratio is 1.6 at 1 hour after tracer injection, and **C** Tomographic reconstruction of SPECT myocardial perfusion images confirming significant myocardial uptake of the isotope, with no blood pool activity.

With regard to symptoms, angina pectoris in our patient could likely be multifactorial from a combination of preexisting atherosclerotic epicardial CAD, and cardiac amyloidosis leading to structural (intrinsic and extrinsic) luminal narrowing of epicardial coronaries, and microvascular dysfunction. Light-headedness could be caused by a combination of arrhythmias (like atrial fibrillation), conduction disturbance (like high-grade atrioventricular block), and profound orthostatic hypotension associated with neuropathy, as occurred in our patient.[5] Although absent in this case, dynamic left ventricular outflow tract obstruction due to basal septal hypertrophy can also lead to hypotension and even syncope.[6] Elevated levels of troponin-I and brain natriuretic peptide are commonly seen in patients with CA due to myocardial ischemia (mechanisms as described previously) and elevated LV filling pressures, respectively, and portend a poor prognosis.[7–9] Atrial fibrillation is one of the most common rhythm abnormalities in CA and results from to both significant left atrial dilation secondary to restrictive cardiomyopathy and atrial deposition of amyloid. In addition, atrial fibrillation with slow ventricular response and other conduction disturbances may arise due to amyloid protein deposition in the sino-atrial node and elsewhere in the conduction system.[5,10]

While low-voltage ECG is common among patients with AL amyloidosis, only a minority with ATTR have low voltage on ECG.[11] Long-standing preexisting hypertension (as in our patient) in CA may also lead to a 'normal' QRS voltage on ECG due to underlying true LV myocardial fiber hypertrophy prior to myocardial amyloid deposition. Traditionally described ECG and echocardiographic features have reduced sensitivity and specificity for identifying ATTR.[11] Apical sparing pattern of LV longitudinal strain on speckle tracking

echocardiography has been shown to have a high accuracy for identifying CA from other causes of increased LV thickness,[1,12,13] and has the potential to guide referral for confirmative testing with Tc-PYP imaging, which has a high specificity for diagnosing ATTR.[14]

Bone avid radiotracers like pyrophosphate were initially used for myocardial infarction imaging. The most reliably understood underlying mechanism is the binding of these bone scintigraphy tracers to cardiac microcalcifications.[15] With amyloidosis, a calcium-dependent P-component binds the amyloid fibrils together, and this provides the likely pathophysiological mechanism for positive PYP scans. It is the pattern of PYP uptake that differentiates the diagnoses, where uptake is diffuse in cardiac ATTR and regional in infarction.[15] This mechanism also rationalizes the described borderline uptake of PYP in AL cardiac amyloidosis,[14] making it imperative to be excluded prior to establishing a diagnosis of ATTR cardiac amyloidosis. A positive Tc-PYP scan along with negative immunoglobulin light chain assays is now the considered diagnostic for ATTR.[16]

Management of CA involves a twofold approach encompassing the control of cardiac symptomatology and treatment of the underlying disease mechanism. Multidisciplinary supportive care is critical in managing symptoms. Regardless of the type of CA (ATTR or AL) some general cardiac management ideologies exist. Many standard medical regimens, such as BB and ACEi/ ARB, which form the cornerstone of therapy in patients with heart failure with reduced ejection fraction and atrial fibrillation, can be potentially toxic in patients with coexisting CA, and should be initiated with great caution.[11] Restrictive cardiomyopathy in patients with CA results in a fairly fixed stroke volume, and therefore, heart rate augmentation is the main mechanism to increase cardiac output. Most elderly patients already have an impaired heart rate response due to the aging process, which is further compromised by neuropathic processes in CA. Therefore adding BB, even in small doses, to this already weakened autoregulatory mechanism, may cause undesirable significant negative chronotropic and inotropic effects. These patients have considerably reduced vascular tone in addition to concomitant sympathetic dysfunction related to transthyretin deposits, and therefore medications that act via angiotensin blockade (ACEi/ARB) may lead to hypotension and not be tolerated. This turned out to be the case in our patient who developed profound orthostatic hypotension with small doses of a BB and ACEi, which eventually had to be discontinued. Furthermore, certain calcium channel blockers and digoxin bind to amyloid fibril deposits,which can lead to potential toxicity. This may manifest as amplified negative inotropic effects, high-grade AV blocks, and even shock.[17–19] Diuretics remain the mainstay of treatment in patients with CA, as found in this case.

In addition to general management strategies, there are multiple new therapies available for ATTR now. Broadly, these can be classified as (a) TTR stabilizers like diflunisal, a nonsteroidal[20] and more recently Tafamidis, a benzoxazole derivative lacking nonsteroidal anti-inflammatory drug activity[21] that stabilizes TTR from breaking down into amyloidogenic monomers; (b) TTR silencers like Patisiran,[22] a specific small interfering ribonucleic acid that inhibits TTR protein synthesis or Inotersen,[23] an oligonucleotide inhibitor of the hepatic production of transthyretin protein; and (c) TTR degraders and extractors of already deposited amyloid protein, such as a combination of Doxycycline and bile salt and tauroursodeoxycholic acid.[24] More evidence is required for proving the efficacy of these novel therapies for ATTR in improving cardiovascular symptoms and outcomes. Till then, for management of heart failure symptoms, which are primarily caused by volume overload, diuretics remain the mainstay of therapy.

Disclosures

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