Case Report

Delayed diagnosis of cardiac amyloidosis in a West African octogenarian

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Abstract

Left ventricular hypertrophy (LVH) is a common finding on cardiac imaging. Although there are multiple aetiologies for LVH, hypertension is frequently a presumed cause due to its high prevalence in the African region. Establishing a specific cause of LVH however requires thorough clinical evaluation with multimodality cardiac imaging playing a key role in the diagnostic pathway. We report on a case of a West African octogenarian who was treated presumptively for heart failure with preserved ejection fraction from hypertensive heart disease, based on his initial clinical presentation and echocardiographic findings three years earlier. By adopting a stepwise approach to his evaluation, including revisiting the history, and the application of multimodality cardiac imaging, the patient was diagnosed with cardiac amyloidosis.

Keywords: left ventricular hypertrophy, cardiac amyloidosis, heart failure, West Africa

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Left ventricular hypertrophy (LVH) is a common echocardiographic diagnosis.[1] This finding defines the pathophysiological basis of disease but does not reliably establish the underlying cause.[2] Therefore, LVH diagnosed on echocardiography should prompt a search for the specific underlying cause to guide patient care.[2]

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In the African region, hypertensive heart disease is common and is driven by the rising prevalence of hypertension.[1] The discovery of LVH in the presence of hypertension therefore frequently leads to a presumptive diagnosis of hypertensive heart disease without a systematic search for alternative causes.

The causes of LVH include but are not limited to aortic stenosis, hypertension, hypertrophic cardiomyopathy (HCM) and infiltrative cardiomyopathies such as Fabry's disease and cardiac amyloidosis.[3] Cardiac amyloidosis is emerging as an important cause of LVH.[4]

Cardiac amyloid is the cardiac manifestation of systemic amyloidosis in which misfolded proteins aggregate into β-amyloid fibrils and deposit in the interstitium between cardiac myocytes.[3] Patients in advanced stages of the disease tend to have restrictive cardiomyopathy (CM) with progressive organ dysfunction and failure.[3,5]

Cardiac amyloidosis is designated light-chain amyloid cardiomyopathy (AL-CM) and transthyretin amyloid cardiomyopathy (ATTR-CM), depending on the culprit amyloidogenic precursor protein. ATTR-CM is further designated as wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) for the wild-type, and variant transthyretin cardiomyopathy (ATTRv-CM) for the mutant type.[3]

The ATTRwt-CM subtype occurs more commonly in the elderly, with distinct clinical features and disease course.[4] Although the pathology is predominantly cardiac, extracardiac tissue can also be affected.[4] Due to the multisystem manifestation of the disease, clinicians may be led down alternative diagnostic pathways, sometimes leading to diagnostic delays and misdiagnoses.[3,6]

ATTRwt-CM is an important cause of undiagnosed heart failure, usually presenting as heart failure with preserved ejection fraction (HFpEF) and dysrhythmias in men above 60 years of age.[4] This case highlights the need for a high index of suspicion to facilitate timely diagnostic evaluation and appropriate treatment. This is imperative, given recent therapeutic advances that have a positive impact on patient survival, functional capacity and quality of life.

Case report

We present an 81-year-old male who came in to our facility with a three-week history of progressive bipedal swelling, scrotal swelling and exertional dyspnoea alongside complaints of cough, orthopnoea, palpitations and symptoms consistent with prostatism. He had a 10-year history of adequately controlled hypertension. He had also developed bilateral carpal tunnel

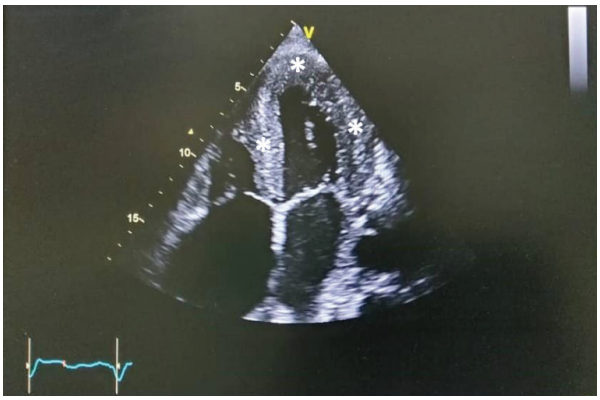

Fig. 1. Apical four-chamber view showing speckled appearance of the myocardium, severe concentric LVH (white stars) with thickening of the right ventricular and atrial walls.

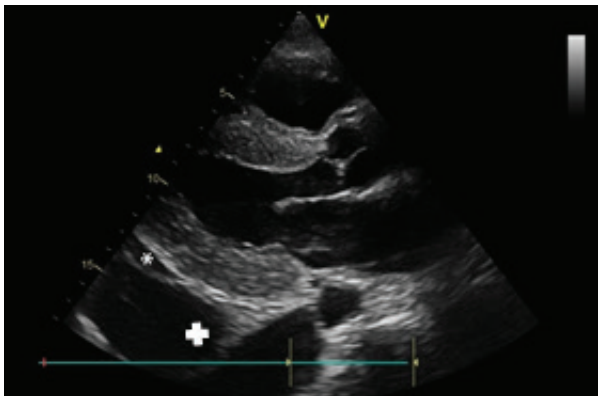

Fig. 2. Parasternal long-axis view showing the speckled appearance of the myocardium, mild pericardial effusion (white star) and a large pleural effusion (white cross).

syndrome four years earlier, for which he had carpal tunnel release surgery. Three years prior to the index presentation, he was diagnosed with HFpEF after presenting with suggestive symptoms. At the time, his echocardiogram revealed severe concentric LVH and a diagnosis of hypertensive heart disease was made.

Diuretic therapy, an angiotensin-converting enzyme inhibitor (ACEI) and a beta-blocker were initiated. He developed mild renal impairment, which had been non-progressive over a period of three years. The index admission was due to worsening symptoms of heart failure. On physical examination, the patient was acutely ill with an irregularly irregular pulse, features of systemic and pulmonary congestion as well as bilateral pleural effusion consistent with acute decompensated heart failure.

His ECG showed atrial fibrillation, a pseudo-infarct pattern in the inferior leads and low-voltage QRS complexes in all leads. An echocardiogram done at our facility showed a speckled appearance of the myocardium with diffuse thickening of all walls of the heart (more prominent in the ventricles), non-dilated ventricles and bi-atrial dilatation (Fig. 1). A mild pericardial effusion and bilateral pleural effusion were observed (Fig. 2). There was global hypokinesia with relative sparing of the apex and severe left ventricular (LV) systolic dysfunction (ejection fraction 21%).

Echocardiographic speckle-tracking strain analysis showed markedly reduced global longitudinal strain (–1.9%) with relative sparing of the apex (Fig. 3). A chest X-ray showed bilateral pleural effusion. Cardiac magnetic resonance imaging showed an increased LV mass (111 g/m^2) and a diffuse pattern of late gadolinium enhancement with a failure to null in look-locker sequences, typical of cardiac amyloidosis (Fig. 4). Multimodality cardiac imaging findings were strongly suggestive of cardiac amyloidosis.

Blood work-up (Table 1) revealed mild normochromic normocytic anaemia, a cholestatic pattern of hepatic injury and mild renal impairment, which was unchanged from baseline. His prostate-specific antigen was normal with mild prostamegaly on ultrasonography.

Based on the patient's clinical presentation, investigation results and multimodality cardiac imaging findings, a presumptive diagnosis of decompensated heart failure secondary to cardiac amyloidosis with atrial fibrillation was made. ATTRwt-CM was considered the most likely cause on account of his age, insidious clinical course and history of carpal tunnel syndrome.

His heart failure medications were adjusted. The beta-blocker and ACEI were withdrawn on account of episodes of hypotension and the possibility of autonomic dysfunction, which can occur with ATTRwt-CM. He was maintained on low doses of a diuretic (furosemide 40 mg daily). Anticoagulation was initiated (rivaroxaban 20 mg daily) on discussion with caregivers based on a CHA_2DS_2VASc score of 4 and a HASBLED score of 4 (hypertension was well controlled and mild renal impairment was non-progressive).

Our patient presented with end-stage disease evidenced by multisystem involvement and hence the prognosis was guarded. His relatives were therefore counselled appropriately. Unfortunately, the patient suffered cardiac arrest in hospital and did not respond to resuscitative efforts.

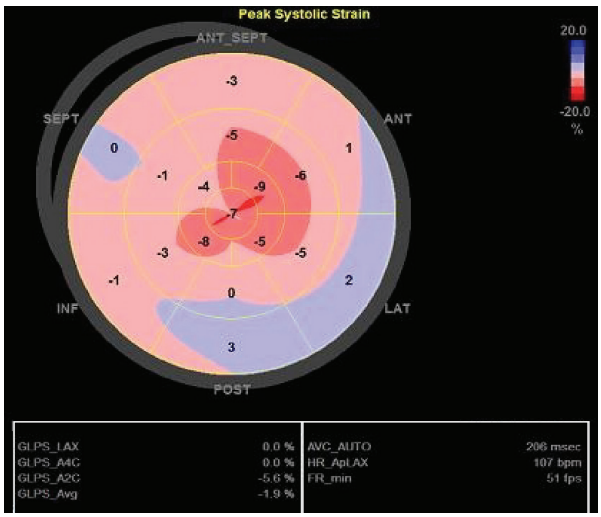

Fig. 3. Echocardiographic speckle-tracking strain analysis showed markedly reduced global longitudinal strain (–1.9%) with relative sparing of the apex.

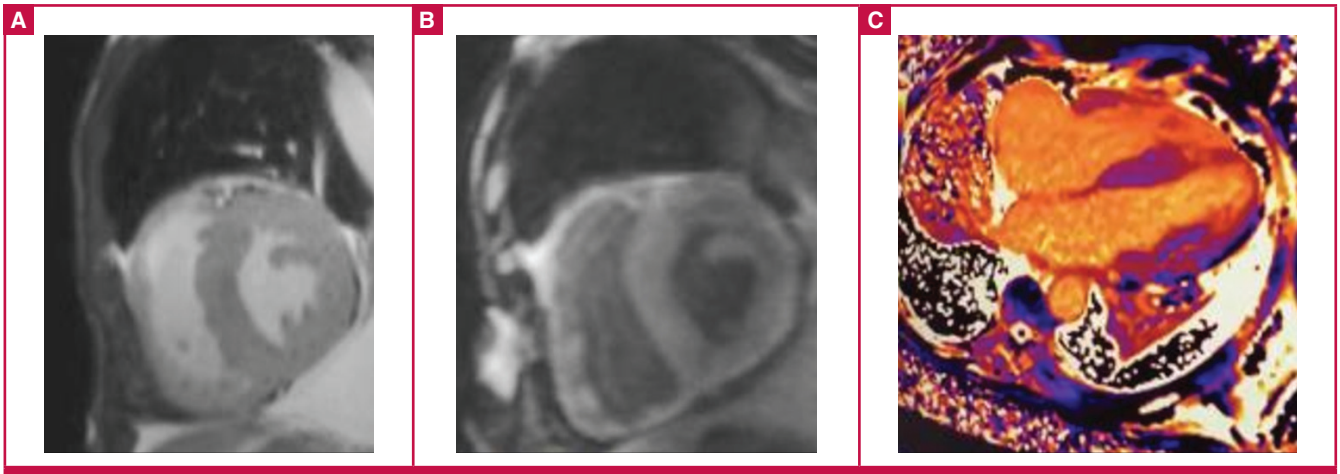

Fig. 4. Cardiac MRI showing hypertrophy of the walls of both ventricles (A). Diffuse pattern of late gadolinium enhancement throughout the myocardium with a failure to null in look-locker sequences (B) with positive T1 values (C).

Discussion

Although the wild-type of ATTR-CM is the most commonly reported type of ATTR-CM, the precise incidence and prevalence in different geographic regions is unknown.[7] Existing patient registries however suggest that the disease is predominantly found in elderly male Caucasians above the age of 80 years.[7] Among patients with ATTRv-CM in the United States, the most common mutation, Val122Ile (pV142I), appears to be exclusive to individuals of West African descent.[7] The disease phenotype is strikingly similar to ATTRwt-CM, with symptom onset around the age of 69 years.[7]

ATTRwt-CM is largely a disease of elderly males.[4] Historically, octogenarians have been frequently affected with a more dismal prognosis due to age-related co-morbidities, as seen in this case.[8,9] Females and younger patients can however also be affected.[4,10] In a study by Grogan *et al*., the youngest affected patient was 47 years, challenging the notion that ATTRwt-CM is solely a disease of the elderly.[4] A few decades ago, ATTRwt-CM was more commonly identified at post mortem due to the insidious disease course and resultant ante-mortem diagnostic delays.[4,6]

Over 60% of patients present with symptoms of heart failure at diagnosis, as was the case in our patient.[10] In low-resource settings, the ECG can provide initial diagnostic clues. Discordance between QRS voltages and the degree of LVH may be observed, as seen in our patient.[3] However, low-voltage QRS complexes are a relatively late finding, with low sensitivity, found in only about 30% of patients with cardiac amyloid.[3,11]

Atrial fibrillation/flutter and conduction abnormalities are common,[10] with atrial arrhythmias reported as a presenting feature in approximately two-thirds of patients, as seen in our patient.[4,10] Atrial arrhythmias result from atrial remodelling, caused by amyloid infiltration of atrial tissue and concomitant dilatation of the atrium.

Nearly half of these patients develop carpal tunnel syndrome, often bilateral, five to 10 years before a diagnosis of ATTRwt-CM is made.[6,10] In this case, the diagnosis of carpal tunnel syndrome preceded the onset of symptoms by four years. Tenosynovial tissue biopsy at the time of carpal tunnel release surgery may facilitate an early diagnosis,[12] however we found no record of a prior histopathological diagnosis in our patient. Sood *et al.* observed a low diagnostic yield with tenosynovial tissue biopsy; a cumulative incidence of 0.55% of amyloidosis at 10 years in patients undergoing carpal tunnel release surgery.[12]

Although the pathology is predominantly cardiac, other organs may be involved, although less frequently.[10] Our patient probably had infiltration of the liver, pleura and prostate on account of the presence of cholestatic hepatic injury, bilateral pleural effusion and prostamegaly, respectively.

Although the clinical course of patients with ATTRwt-CM is fairly distinctive, as described in our patient, it is important to rule out AL amyloidosis and familial ATTR amyloidosis for a tailored therapeutic approach. Notably, patients with

Table 1. Laboratory investigation results

Variables	*Baseline*	*Repeat*	*Reference range*
Full blood count			
Haemoglobin, g/dl	11.8		11.0–18.0
Platelet count, 10^9 cells/l	134.0		150.0–450.0
Total white cell count, 10^9 cells/l	7.8		2.5–8.5
Renal function			
Sodium, mmol/l	134.0	130.0	135.0–150.0
Potassium, mmol/l	5.0	5.2	3.5–5.5
Chloride, mmol/l	97.0	99.0	95.0–110.0
Urea, mmol/l	14.5	15.3	2.0–7.0
Creatinine, µmol/l	124.0	120.0	71.0–133.0
eGFR (ml/min/1.73 m^2)	63.0	65.0	> 89.0
Liver function test			
Total bilirubin, µmol/l	49.4		
Direct bilirubin, µmol/l	33.3		0.0–5.0
Aspartate transaminase, U/l	33.0		15.0–46.0
Alanine transaminase, U/l	19.0		13.0–69.0
Alkaline phosphatase, U/l	259.0		38.0–129.0
Gamma glutamyl transferase, U/l	194.0		12.0–58.0
Total protein, g/dl	70.0		63.0–82.0
Albumin, g/dl	32.0		35.0–50.0
Lipid profile			
Total cholesterol, mmol/l	3.10		3.30–6.20
LDL cholesterol, mmol/l	2.01		0.00–3.90
HDL cholesterol, mmol/l	0.57		1.03–1.55
Triglycerides, mmol/l	1.26		0.40–2.25

eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

ATTRwt-CM may have an associated monoclonal gammopathy, with no evidence of immunoglobulin light chains on biopsy, highlighting the need for biopsy for appropriate amyloid protein subtyping.[6] ATTRv-CM can be distinguished from ATTRwt-CM by sequencing of the TTR gene.[10]

Multimodality cardiac imaging plays a significant role in diagnosis, as demonstrated in our case. Of key importance is the observation of reduced LV systolic function in the presence of normal cardiac chamber sizes, which is consistent with cardiac amyloidosis but inconsistent with end-stage hypertensive heart disease. This pattern was similarly observed by Grogan and colleagues.[4] In the absence of a monoclonal gammopathy, nuclear scintigraphy with technetium-labelled bisphosphonate is highly sensitive (99%) and specific (86%) for ATTR cardiac amyloidosis.[10]

The patient's untimely demise limited our ability to perform further evaluation to accurately subtype his cardiac amyloidosis. However, based on his clinical trajectory, we considered a diagnosis of ATTRwt-CM to be most likely. As he presented with advanced disease involving multiple systems, further diagnostic evaluation to subtype his disease would have been beneficial based on his preferences and values. Emerging therapeutic options for ATTRwt-CM include tafamidis, a tetramer stabiliser, which is most effective when given in the early stages of the disease.[10,13] Otherwise, the prognosis of ATTRwt-CM remains dismal, especially when diagnosis is delayed.[4]

Conclusion

ATTRwt-CM may initially present with LVH and HFpEF in the elderly. It should therefore be considered a plausible differential diagnosis in the appropriate clinical context, irrespective of a history of long-standing hypertension. Multimodality cardiac imaging plays a key role and should be utilised as appropriate to help establish the diagnosis. With increasing awareness and a high index of clinical suspicion, it may be possible to detect ATTRwt-CM in the early stages of the disease. The diagnostic pathway should include more sensitive and specific diagnostic tools such as cardiac scintigraphy, in the absence of a monoclonal gammopathy, and genetic testing, to aid in the early detection of ATTRwt-CM.

Early diagnosis is crucial as current therapeutic options have value largely in the early stages of the disease. In low-resource settings however, lack of specialist expertise results in low recognition of ATTRwt-CM, and cost and limited availability of advanced diagnostic tools and pharmacotherapy make early diagnosis and management challenging.

We can surmount these challenges by improving care-provider awareness of the disease to increase clinical suspicion of ATTRwt-CM in the early stages, improving early diagnostic capacity by making additional diagnostic tools such as cardiac scintigraphy and genetic testing more available and affordable, and working to make novel therapeutic options for cardiac amyloidosis affordable and available in low-resource settings.

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