JACC: CASE REPORTS VOL. 1, NO. 2, 2019

CASE REPORT

BEGINNER

CLINICAL CASE

Evaluating Suspected Cardiac Amyloidosis

Manish Motwani, MBChB, PhD,[a,b] Parthiban Arumugam, MBBS, MSc,[c] Alberto Rocci, MD, PhD,[d,e] Luigi Venetucci, MBChB, PhD[a,b]

ABSTRACT

A 71-year-old-woman presented with breathlessness, general tiredness and orthopnea. Echocardiography and electrocardiogram were suspicious for cardiac amyloidosis. This case illustrates contemporary evaluation to confirm the diagnosis and distinguish between different types of amyloid. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2019;1:141–5) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 71-year-old woman presented with a 3-month history of progressive dyspnea, general tiredness, and orthopnea. Pro-B-type natriuretic peptide was raised and there were clinical signs of heart failure (HF) with bibasal crepitations and ankle edema. Blood pressure and heart rate were normal; but clinically the patient was in atrial fibrillation (AF).

PAST MEDICAL HISTORY

The patient experienced carpal tunnel syndrome 15 years ago.

LEARNING OBJECTIVES

- Recognize the clinical, imaging, and ECG features of cardiac amyloidosis.
- Recall the common types of cardiac amyloid and how to distinguish between them.

DIFFERENTIAL DIAGNOSIS

The most common cause of new onset HF in the elderly is ischemic cardiomyopathy, but there was no history of myocardial infarction or preceding angina. Aging is itself associated with reduced aortic and left ventricular (LV) compliance, increased aortic impedance, and abnormal LV diastolic function. These age-related changes lower the threshold for developing HF when exposed to common precipitating factors such as hypertension or arrhythmias (especially AF), and this was the initial suspected etiology until first-line investigations were completed.

INVESTIGATIONS

Transthoracic echocardiography (TTE) was suspicious for an infiltrative process such as cardiac amyloidosis (CA) with severely impaired LV systolic function, severe diastolic dysfunction (restrictive physiology),

From the [a]Manchester Heart Centre, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, United Kingdom; [b]Institute of Cardiovascular Sciences, University of Manchester, Manchester, United Kingdom; [c]Nuclear Medicine Centre, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, United Kingdom; [d]Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom; and the [e]Department of Clinical Haematology, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, United Kingdom. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 25, 2019; accepted June 27, 2019.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.06.027

ABBREVIATIONS AND ACRONYMS

AL = light-chain amyloidosis

ATTR = amyloid transthyretin

CA = cardiac amyloidosis

DPD = 2,3-dicarboxypropane-1,1-diphosphonate

ECG = electrocardiogram

FLC = free light chain

LV = left ventricular

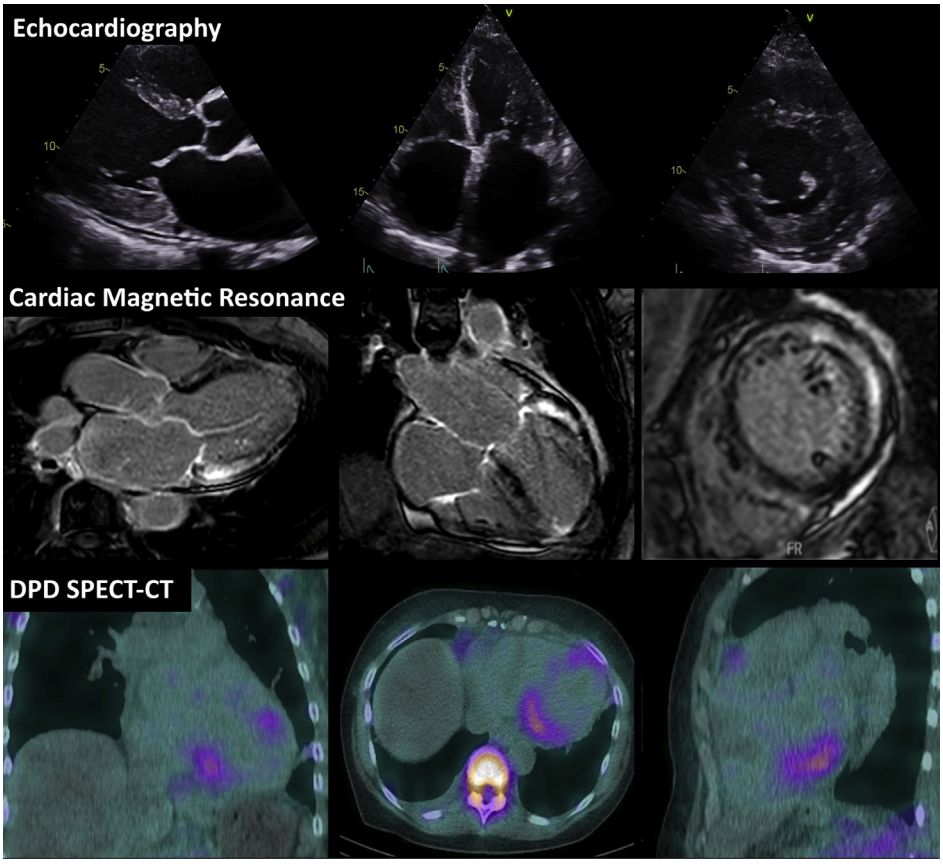
LVH = left ventricular hypertrophy

SPECT = single-photon emission computed tomography

TTE = transthoracic echocardiography

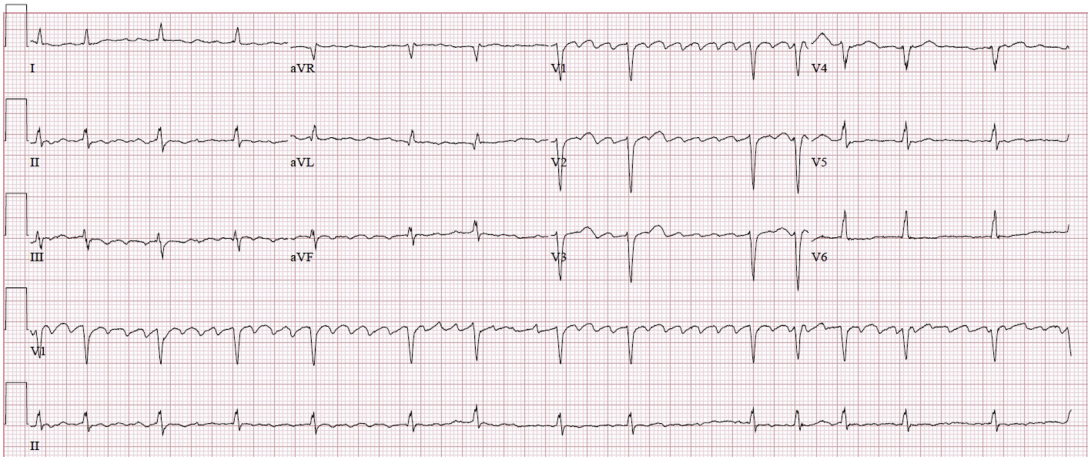
moderate concentric LV hypertrophy (LVH), severely dilated atria, thickened atrial septum, thickened valves, and a small pericardial effusion (Figure 1). There was no hypertension to account for the LVH, and an electrocardiogram (ECG) did not satisfy voltage criteria for LVH. This discrepancy also favored an infiltrative process such as CA. Additional ECG findings were low-voltage complexes in the limb leads and pseudoinfarct pattern in the anterior chest leads (Figure 2). Both are typical ECG features of CA seen in ~60% and ~50% of cases respectively (both together in ~25%) (1,2). Finally, AF was present which is also common in CA. Atrial arrhythmias are seen in 10% to 15% (1,2). Cardiac magnetic resonance (CMR) confirmed the TTE findings and also demonstrated extensive diffuse myocardial infiltration on late gadolinium enhancement consistent with CA (Figure 1). Specialist hematology consultation led to serum and urine electrophoresis, immunofixation, and serum free light chain (FLC) assay. High levels of circulating kappa and lambda FLCs, abnormal FLC ratio, and a serum paraprotein (but too low to quantify) favored systemic light-chain amyloidosis (AL). However, because of the patient's age and possibility of hematology results being incidental or a monoclonal gammopathy of unknown significance, exclusion of transthyretin amyloidosis (amyloid transthyretin [ATTR]) was still recommended using single-photon emission computed tomography (SPECT) with 2,3-dicarboxypropane-1,1-diphosphonate (DPD). Despite the extent of infiltration seen on CMR, the DPD-

FIGURE 1 Cardiac Imaging in Amyloidosis



Echocardiography **(top row)** shows moderate concentric left ventricular hypertrophy, severely dilated atria, small pericardial effusion, thickened interatrial septum, and thickened valves. Late gadolinium enhancement with cardiac magnetic resonance **(middle panel)** shows extensive heterogeneous myocardial enhancement consistent with diffuse amyloid infiltration. Comparatively low-grade uptake (Perugini grade 1) with 2,3-dicarboxypropane-1,1-diphosphonate (DPD) on hybrid single-photon emission computed tomography/computed tomography (SPECT-CT) **(bottom row)** favors light-chain amyloid, which was subsequently confirmed on bone marrow biopsy.

FIGURE 2 Typical Electrocardiogram Features of Cardiac Amyloidosis



Low-voltage limb leads with absent left ventricular hypertrophy voltage criteria despite increasd wall thickness on echocardiography, pseudo-infarction in anterior precordial leads, and coarse atrial fibrillation.

SPECT scan showed only minor cardiac uptake (Perugini grade 1: cardiac uptake less intense than bone signal) (**Figure 1**). This finding favored AL because DPD is much more avidly taken up by infiltrated myocardium in ATTR (Perugini grade 2 or 3) (1–3). Subsequent bone marrow biopsy confirmed AL with a monoclonal plasma cell infiltration of >40%.

MANAGEMENT

She has responded extremely well to 4 cycles of chemotherapy (velcade, cyclophophamide, dexamethasone) and at 12 months from initial diagnosis she is considered to be in complete serological remission. Although her LV systolic function remains severely impaired, she has noted a substantial improvement in HF symptoms and is able to walk on the flat with ease, enjoys ballroom dancing, and is only limited with inclines or prolonged activity.

DISCUSSION

Amyloid is an amorphous, fibrillar proteinaceous material that can be formed from several different precursor proteins (**Table 1**), but the common forms that result in cardiac deposition are AL and ATTR (1–3).

AL is a hematologic disorder of plasma cells closely related to but distinct from multiple myeloma. It is caused by the proliferation of an abnormal clone of plasma cells that overproduce lambda or, less commonly, kappa light chains. It is a multiorgan disease, although one organ system usually predominates: most commonly, it is renal involvement with nephrotic syndrome, and cardiac involvement with cardiomyopathy is the second most common (1). Other organ systems that may be involved include the peripheral and autonomic nervous system, vasculature, liver and gastrointestinal tract, and soft tissues.

ATTR may be wild-type, derived from structurally normal transthyretin, or familial, derived from a mutant form, of which >80 amyloidogenic mutations have been described (3). Patients with wild-type ATTR almost invariably present with clinically isolated cardiomyopathy, but the condition was formerly known as senile systemic amyloidosis because of the subclinical involvement of other organs noted at autopsy (commonly, the lungs and gastrointestinal tract) and a high prevalence of carpal tunnel syndrome due to infiltration. Patients with familial ATTR tend to express a phenotype specific to their particular mutation, with neuropathy-predominant, cardiac-predominant, and mixed phenotypes all identified in different family clusters (3).

Precise definition of the precursor protein causing amyloid deposition is essential because the different forms of amyloidosis have differing clinical courses and completely different therapies. **Figure 3** summarizes a simple 4-step contemporary

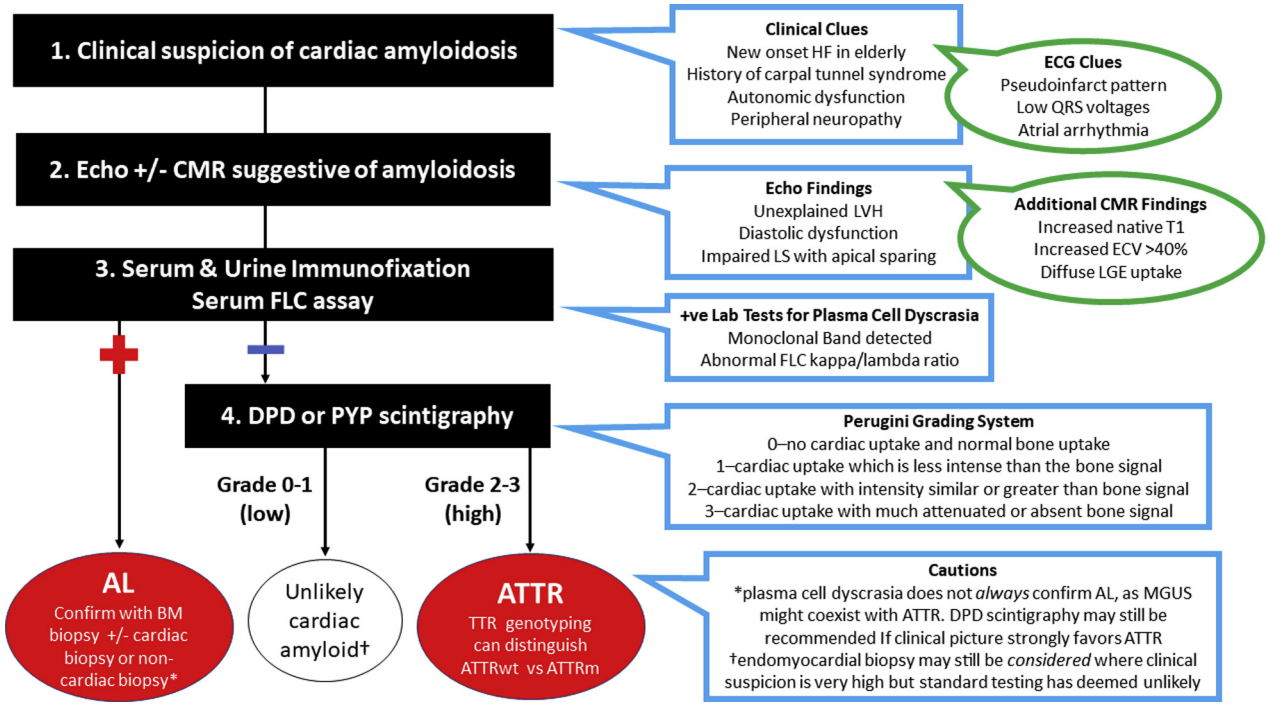
TABLE 1 Most Common Forms of Cardiac Amyloidosis

Amyloid Type	Etiology	Precursor Protein	Typical Age (yrs)	Clinical Clues	Median Survival (yrs)
AL	Plasma cell dyscrasia	Light chains	>50	Kidney, heart, and liver involvement Peri-orbital bruising Macroglossia Severe hypotension with ACE inhibitor	1–3
ATTRwt	Old age	Wild-type normal TTR	>75	Isolated cardiac involvement Male dominance Carpal tunnel syndrome 5–10 yrs prior	4–6
ATTRm	Familial mutation of TTR	Mutant TTR	>40 60–65 (V1221 variant)	African American/Caribbean (V1221 variant) Cardiac, polyneuropathy or mixed depending on mutation.	2

ACE = angiotensin-converting enzyme; AL = light-chain amyloidosis; ATTRm = familial amyloid transthyretin; ATTRwt = wild-type amyloid transthyretin; TTR = transthyretin.

approach to confirming CA and distinguishing between AL and ATTR. An interesting aspect in this case was the presentation with isolated cardiomyopathy in old age (no evidence of multi-organ involvement) and prior carpal tunnel syndrome, which all favored ATTR type; therefore, despite finding a paraprotein, it was still felt pertinent to exclude ATTR with DPD-SPECT (as is recommended in such scenarios) in case the paraproteinemia was an incidental monoclonal gammopathy of unknown significance or coexistent pathology (1–3).

FIGURE 3 Four-Step Algorithm for Evaluating Suspected Cardiac Amyloidosis



A summary flowchart and explanatory notes for contemporary evaluation of suspected cardiac amyloidosis (diagnosis and typing). +ve = positive; AL = light-chain amyloidosis; ATTR = amyloid transthyretin; ATTRm = familial amyloid transthyretin; ATTRwt = wild-type amyloid transthyretin; BM = bone marrow; CMR = cardiac magnetic resonance; DPD = 2,3-dicarboxypropane-1,1-diphosphonate; ECG = electrocardiogram; ECV = extracellular volume; FLC = free light chain; HF = heart failure; LGE = late gadolinium enhancement; LS = longitudinal strain; LVH = left ventricular hypertrophy; MGUS = monoclonal gammopathy of unknown significance; PYP = pyrophosphate; TTR = transthyretin.

Until recently, CA was viewed as a rare, largely untreatable condition, and often only diagnosed at autopsy. However, major advances have been made over the last decade, both in diagnosis and treatment of CA, along with a recognition that the condition is more common than previously believed (4). Along with supportive treatment for the organ systems involved, both AL and ATTR now have specific treatment strategies (1-3,5,6). In AL, high-dose chemotherapy (and sometimes stem cell transplant) regimens similar to those for multiple myeloma are used to reduce the number of abnormal plasma cells and reduce production of FLCs (1). In ATTR, which was previously treatable only by organ transplantation, pharmaceutical therapy that slows or halts ATTR cardiomyopathy progression is now available with favorable clinical outcomes (e.g., tafamidis) (3,5,6). In both forms of CA, early recognition remains essential to afford the best treatment efficacy.

CONCLUSIONS

This case highlights typical imaging and ECG features in CA and illustrates a contemporary approach to confirming diagnosis and amyloid type. In general, the approach involves TTE and CMR followed by a combination of hematology tests, biopsy, and DPD-SPECT to distinguish AL and ATTR types.

ADDRESS FOR CORRESPONDENCE: Dr. Manish Motwani, Manchester Heart Centre, Oxford Road, Manchester University NHS Foundation Trust, Manchester M13 9WL, United Kingdom. E-mail: mani.motwani@mft.nhs.uk. Twitter: @Doc_Tiger.

REFERENCES

1. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol 2016;68:1323–41.

2. Falk RH, Dubrey SW. Amyloid heart disease. Prog Cardiovasc Dis 2010;52:347–61.

3. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2019;73:2872–91.

4. Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Adv 2018;2:1046–53.

5. Maurer MS, Schwartz JH, Gundapaneni B, et al., ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007–16.

6. Liu PP, Smyth D. Wild-type transthyretin amyloid cardiomyopathy: a missed cause of heart failure with preserved ejection fraction with evolving treatment implications. Circulation 2016;133:245–7.

KEY WORDS cardiac magnetic resonance, echocardiography, electrocardiogram, imaging, nuclear medicine, restrictive