



Cardiac amyloidosis- untangling the facts

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Introduction

Cardiac amyloidosis is a rare but often overlooked cardiomyopathy which can have a prognosis worse than metastatic cancer if left untreated¹ and may result in sudden cardiac death².

More prevalent than first thought, and with rapid advances in cardiac imaging as well as promising new therapies; it is essential that cardiologists have a good understanding of this condition. It is particularly important to know when to suspect cardiac amyloidosis, the investigation findings that will allow its diagnosis, and the principles of its management.

Basic pathophysiology

Amyloidosis is a condition characterised by the extracellular deposition of misfolded protein or 'amyloid fibrils'. Normal circulating serum proteins (or their components) accumulate and aggregate (taking up β -pleated sheet configuration) into insoluble fibrils which in turn result in tissue and organ dysfunction via direct cellular toxicity, infiltration or both.

There are over 30 different amyloidogenic proteins in humans³ leading to different types of local and systemic amyloidosis (e.g. β_2 microglobulin and haemodialysis-associated amyloidosis). However only two types- AL and TTR amyloidosis - account for the vast majority of cardiac amyloidosis cases.

AL amyloidosis

AL or amyloid light chain amyloidosis (previously known as *primary* amyloidosis) is the most common form of systemic amyloidosis⁴ and is caused by plasma cell dyscrasias such as multiple myeloma and MGUS. It is the mass produced light chains which aggregate in this condition. The UK National Amyloidosis Centre sees around 330 new cases of AL amyloidosis each year⁵ but it is widely recognised to be underdiagnosed⁶. It is more prevalent in men and usually manifests in patients whilst in their 50-70s. AL amyloidosis can affect almost any organ, the kidneys and the heart are most frequently affected.

Take Home Messages

- Cardiac amyloidosis is an important yet under-diagnosed cause of heart failure and sudden cardiac death.
- Always consider cardiac amyloidosis in patients with:
 - a) HF-PEF with significant ventricular wall thickening, especially if unexplained
 - b) HF-PEF in the presence of known myeloma/MGUS or suspicion of a multi-system disease
 - c) Ventricular wall thickening on cardiac imaging but a paradoxically low voltage ECG
- Diagnosis requires a multipronged approach, key steps include: investigating for plasma cell dyscrasia, imaging (echo, CMR, radionuclide) and histological confirmation.
- Management involves supportive heart failure treatment, chemotherapy +/- stem cell transplantation for AL cardiac amyloidosis and now Tafamidis for TTR cardiac amyloidosis. Organ transplantation can be performed in exceptional cases.
- Early diagnosis and treatment is vital, as is referral to specialists (local haematology team, National Amyloid Centre) for advanced management.



Cardiac involvement is present in around 50% of cases⁷ and is the most common mode of death in patients⁸. AL cardiac amyloidosis is the most difficult type to treat and is often diagnosed late. Symptomatic AL cardiac amyloidosis carries a poor prognosis with a reported median survival of 6 months if untreated¹.

TTR amyloidosis (ATTR)

In TTR amyloidosis the amyloid protein is transthyretin (TTR). Transthyretin or *prealbumin* as it used to be known, is a naturally abundant circulating serum protein - produced mainly in the liver - which transports thyroxine (T4) and Vitamin A (retinol).

There are 2 types of TTR amyloidosis:

'Wild' type ATTR

In this subtype there is an accumulation and gradual deposition of the normal or 'wild' transthyretin protein over time, hence its other name of senile systemic amyloidosis (SSA). It is mainly seen in older men⁹.

Mutant ATTR

In this group a genetic mutation in the transthyretin gene is responsible for the development of systemic amyloidosis. Over 100 different gene mutations which can be familial and of varying penetrance have now been implicated¹⁰. The most common mutations are TTR V30M and TTR V122I, the latter is particularly prevalent amongst individuals of African-American descent¹¹ where it can be seen in up to 4% of the population and may be the undiagnosed cause of HF-PEF in many.

Between them AL amyloidosis and TTR amyloidosis may account for up to 96% of cardiac amyloidosis cases¹². Other rarer causes include AA amyloidosis and Isolated Atrial Amyloidosis (IAA).

Clinical presentation

Cardiac amyloidosis patients typically present with symptoms and signs of congestive heart failure. In addition to this they may also experience pre-syncope or syncope due to autonomic dysfunction and/or atrioventricular conduction disturbances and palpitations secondary to atrial arrhythmias especially atrial fibrillation.

Extra-cardiac features such as macroglossia, purpura affecting the head and neck and periorbital bruising (fig. 1a) may be recognised by the discerning clinician and are characteristic of AL amyloidosis. Like any significant systemic illness, patients often experience lethargy and weight loss. AL amyloidosis patients can also present with features of the underlying disease process (e.g. multiple myeloma) or of systemic involvement elsewhere in the form of nephrotic syndrome, hepatomegaly or neuropathy. Wild-type ATTR is specifically associated with carpal tunnel syndrome⁹ (often the only extra-cardiac feature) and familial mutant ATTR with sensorimotor and autonomic neuropathy¹³.



Investigations

ECG

Low voltage QRS complexes (defined as QRS amplitude less than 5 mm in limb leads or less than 10 mm in precordial leads) are the hallmark ECG feature of amyloidosis (fig. 1b), especially in AL amyloidosis where it can be seen in 50% of cases¹⁴. Amyloidosis should be suspected in patients with ventricular wall thickening on cardiac imaging but a paradoxically low voltage ECG. Other common features include a pseudo-infarct pattern ('pathological' Q waves with amplitude >25% of QRS in 2 consecutive leads) in the anterior leads, atrioventricular conduction abnormalities and atrial flutter/fibrillation.

Cardiac biomarkers

As in other cardiomyopathies, biomarkers such as NT-proBNP and troponin are commonly raised, and this may be disproportional to the degree of clinical heart failure as it partly reflects the local effect of the amyloid deposits on cardiac tissue¹⁵. Both biomarkers are used to prognosticate and NT-proBNP levels can also be used to determine treatment response in AL amyloidosis¹⁶.

Echocardiography

The classical finding on echo is of ventricular wall thickening (fig. 1c) which is usually concentric, can affect both ventricles, and may also extend to involve the valves. The myocardium may also have an echogenic granular appearance. There is usually significant diastolic dysfunction evident on Doppler assessment often with atrial dilatation, low ventricular volume and evidence of restrictive physiology. Typically left ventricular systolic function is preserved, but in advanced disease systolic impairment can be seen. Pericardial effusions are common (found in 40-60% of cases¹⁷) but are rarely of haemodynamic significance. It is important to note that patients can have normal ventricular wall thickness and still have heart failure (mainly seen in AL amyloidosis) and significant amyloid deposition¹⁸. Advanced echo techniques such as strain and strain rate imaging can be used to distinguish cardiac amyloidosis from other cardiomyopathies as a result of differences in global and regional contractility and relaxation¹⁹.

Magnetic resonance imaging

Cardiac MR has superseded echocardiography as the best imaging modality in the diagnosis of cardiac amyloidosis. It provides earlier and more accurate structural and functional evidence of cardiac amyloidosis, but its real value lies in tissue characterisation using late gadolinium enhancement. Global subendocardial late gadolinium enhancement (fig. 1d) is highly specific for cardiac amyloidosis²⁰ and the extent of this enhancement is also prognostic. Newer diagnostic techniques include measuring the degree of myocardial oedema present on T2 mapping which has also been shown to be a predictor of prognosis in AL cardiac amyloidosis²¹.

Radionuclide imaging

SAP scintigraphy- Developed by the National Amyloid Centre, this radionuclide modality uses I¹²³-labelled serum amyloid P and can be used to assess the total body amyloid



burden²² as well as response to therapy. It is limited in assessing cardiac involvement as there is suboptimal uptake in the moving heart.

^{99m}Tc-DPD scintigraphy- This particular bone tracer has been shown to demonstrate significantly higher myocardial uptake in TTR amyloidosis compared to AL amyloidosis, and combined with the absence of a plasma cell dyscrasia is highly suggestive of TTR amyloidosis²³.

Non-cardiac and endomyocardial biopsy

Histological confirmation (using congo-red staining) and subtyping of amyloid deposition (using immunohistochemistry and/or mass spectrometry) is necessary to diagnose amyloidosis. Non-cardiac biopsies taken from bone marrow and subcutaneous fat can be used and, in addition to clinical and imaging evidence, may suffice to diagnose both AL and TTR amyloidosis. Endomyocardial biopsy however remains the gold standard for a definitive diagnosis of cardiac amyloidosis¹².

Investigating for plasma cell dyscrasia

This is another important step in the diagnostic pathway for (AL) amyloidosis and normally involves performing serum and urine protein electrophoresis, immunofixation and free light chain (FLC) assays as well as a bone marrow biopsy.

Management

As with any other cause of heart failure, it is important to provide supportive therapy (primarily symptom management) and to treat the underlying cause of cardiac amyloidosis. Treatment options for advanced cases may extend to include device therapy and organ transplantation. Patients should be referred to the local haematology team as well as the National Amyloid Centre, especially if there is evidence of cardiac involvement.

Supportive therapy

Diuretics are the mainstay of symptomatic treatment in cardiac amyloidosis. There is no proven benefit from ACE inhibitors/ARBs, and these may lead to significant hypotension in these patients²⁴. Similarly, calcium channel blockers (negatively inotropic) and digoxin (binds to amyloid fibrils increasing the risk of digoxin toxicity²⁵) should generally be avoided. Beta blockers may be helpful in atrial fibrillation, but like other drugs may be poorly tolerated²⁴. Amiodarone can be used for difficult to control arrhythmias²⁶. There is an increased risk of atrial thrombi in cardiac amyloidosis (seen in 33% of amyloid hearts in one autopsy study²⁷) especially in AL amyloidosis, so all patients with atrial fibrillation must be anticoagulated unless contraindicated.

Treating the underlying cause

AL amyloidosis

Multi-agent chemotherapy and stem cell transplantation are the cornerstones of treatment for patients with AL amyloidosis and aim to eradicate clonal plasma cells and by extension light chain production²⁸. Chemotherapy often consists of a combination of alkylators (e.g. melphalan), steroids (e.g. dexamethasone), biological agents (bortezomib) and immunomodulators (e.g. thalidomide)²⁹. Understandably such aggressive treatment carries with it a significant toxicity risk and is therefore not suitable



for all patients. Due to strict eligibility criteria²⁹ (which include age <70, eGFR >50ml/min and low cardiac biomarkers), only a minority of patients receive both chemotherapy and stem cell transplantation³⁰.

TTR amyloidosis

Unlike in AL cardiac amyloidosis which can be treated by targeting the underlying plasma cell dyscrasia, there was no specific treatment for TTR cardiac amyloidosis until recently.

Tafamidis, an exciting new drug which works by stabilising TTR and preventing its breakdown into the monomers that fuel amyloidogenesis has been shown to significantly improve mortality in the landmark ATTR-ACT trial published this year³¹. This multicentre, double blind randomised control trial demonstrated that compared to placebo Tafamidis not only significantly improved 30-day survival (29.5% vs. 42.9%, $p < 0.001$, NNT 8) but also reduced cardiovascular related hospitalisation. Benefits were also seen in functional capacity as measured by 6-minute walk test and quality of life self-assessment scores.

In addition to Tafamidis, Patisiran and Inotersen, two 'RNA interference' drugs (which also disrupt liver production of mutant TTR monomers) are promising new therapies but are still being tested in ongoing trials^{32,33}.

Advanced treatment

Patients with cardiac amyloidosis are more prone to atrioventricular conduction disturbances and can benefit from pacemaker implantation. Offering appropriate patients cardiac resynchronisation therapy as opposed to simple pacing is important as RV pacing may be poorly tolerated. Primary prevention implantable cardiac defibrillators (ICDs) have not been shown to improve survival in cardiac amyloidosis, mainly because electromechanical dissociation (PEA arrest) is the most common mechanism of sudden cardiac death³⁴.

In a very small proportion of patients heart transplantation performed at experienced centres can have good results³⁵. Isolated cardiac involvement (very rare in AL amyloidosis) and fitness for surgery (and subsequent chemotherapy and stem cell transplantation in AL amyloidosis) are vital pre-requisites. In mutant TTR amyloidosis combined heart and liver transplantation (the liver being responsible for producing the amyloidogenic mutant TTR) can be effective and should be considered³⁶.

Conclusion

Cardiac amyloidosis is a rare but underdiagnosed cause of HF-PEF and sudden cardiac death. Due to its typically subtle presentation, diagnosis relies firstly on clinician awareness and then requires multi-modality investigation with echo and CMR playing important roles. Histological confirmation is necessary to confirm the diagnosis. Management is centred around supportive heart failure treatment, with referral to appropriate specialists for specific treatments for AL and TTR amyloidosis. Some patients require device therapy and transplantation may be an option in a select few.



Despite advances in treatment, there is currently no cure for this condition, and by the time it is identified many patients have advanced disease. Early diagnosis and treatment is therefore crucial, and for that reason all cardiologists should be familiar with its presentation, diagnosis and management. To give these patients the best chance, cardiac amyloidosis should not remain an obscure cardiomyopathy recognised by few.

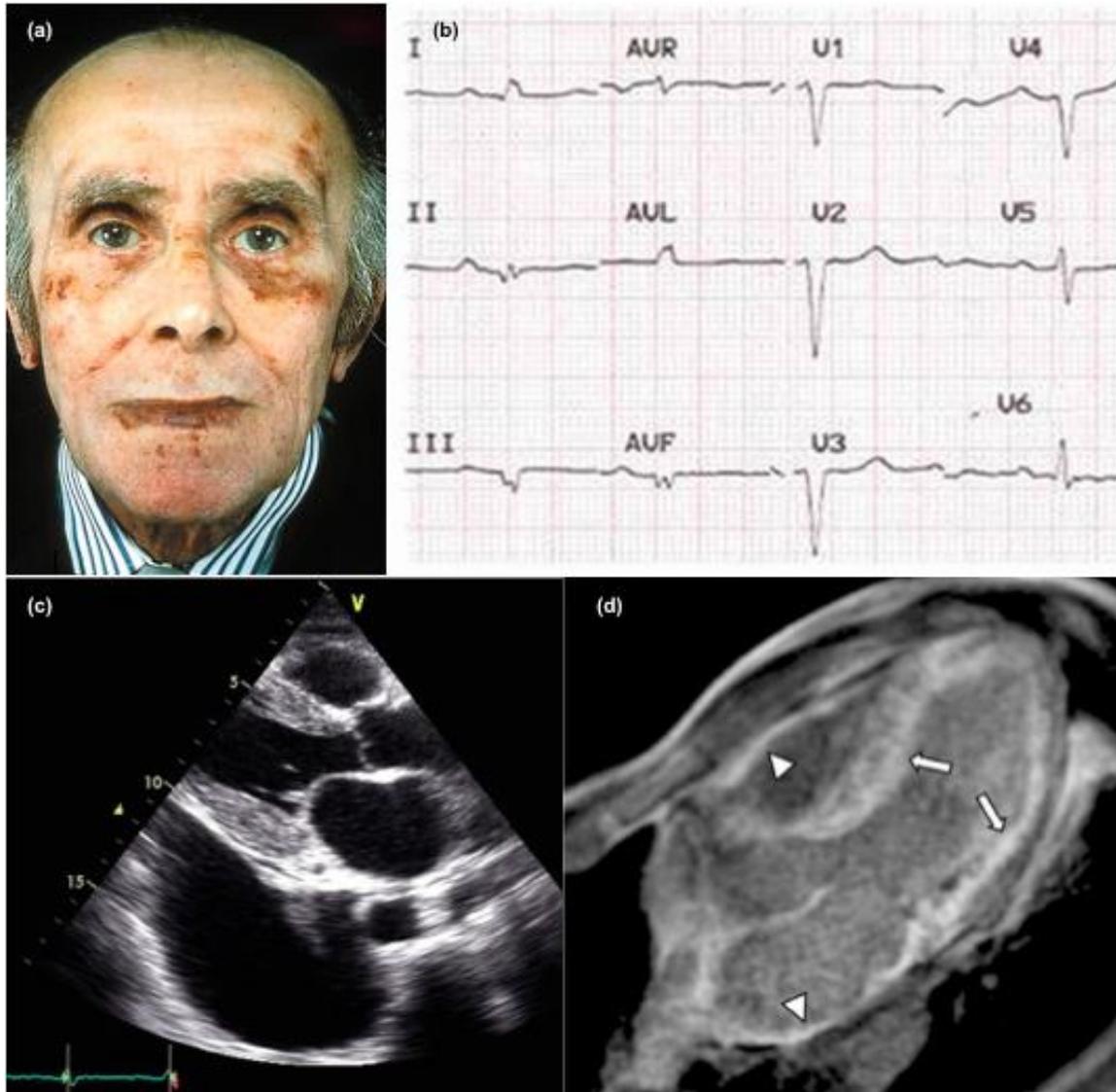


Figure 1. Typical clinical features seen in cardiac amyloidosis: (a) AL amyloidosis patient with periorbital bruising and facial purpura (b) low voltage ECG with pseudo-infarct pattern in the anterior leads (c) parasternal long axis echo image showing ventricular wall thickening, atrial dilatation and pericardial effusion (d) horizontal long axis CMR image of a patient with mutant ATTR showing global left ventricular subendocardial, right ventricular and atrial late gadolinium enhancement (LGE).^{37,38,39,40}



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