

Cardiac amyloidosis

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ABSTRACT – Systemic amyloidosis commonly affects the heart. Indeed, cardiac symptoms may be the first clinical indicator of underlying amyloid deposition. Using two case studies, this article reviews the latest evidence regarding cardiac amyloidosis. The diagnosis of cardiac involvement can be established through imaging with echocardiography and magnetic resonance. Supportive evidence may be gained from biochemical markers such as serum N-terminal pro-brain natriuretic peptide (NT-proBNP). The main clinical consequences of amyloid deposition are cardiac failure and rhythm disturbances. Attempts to cure the underlying disease process with chemotherapy and/or cardiac and/or liver transplantation have had variable results. Stem-cell transplantation is associated with significant mortality in the context of cardiac involvement. Although newer therapeutic agents are emerging, the overall outlook at this time remains poor.

KEYWORDS: amyloid heart disease, amyloidosis, cardiac transplant, heart failure, NT-proBNP, serum amyloid P, stem-cell transplant, transthyretin

Systemic amyloidosis is frequently accompanied by the deposition of amyloid fibrils in cardiac tissue. The term ‘cardiac amyloidosis’ is used to describe the spectrum of disease that may result. Early recogni-

tion of this disease can now facilitate the introduction of proven therapies. The following article reviews the latest literature concerning the diagnosis and management of such patients. It begins with a description of two recent cases that presented to our unit in Manchester.

Case study 1

A 72-year-old man with no significant past medical history presented to Wythenshawe Hospital in 2001 with recurrent chest pain. An electrocardiogram (ECG) exercise tolerance test produced an equivocal result, and subsequent coronary angiography showed no evidence of coronary artery disease. The patient’s chest pain appeared to resolve over subsequent months. He was reassured and discharged from regular follow-up.

In May 2003, he presented with a two-week history of progressive dyspnoea. A chest X-ray on admission demonstrated pulmonary oedema consistent with acute left ventricular failure. The ECG and cardiac enzymes at this time demonstrated no evidence of cardiac ischaemia. He was treated with diuretics and discharged several days later, with plans for outpatient echocardiography.

A transthoracic echocardiogram performed several weeks later demonstrated symmetrical left ventricular hypertrophy, a moderately dilated right ventricle (end-diastolic diameter 5.2 cm), a left ventricular ejection fraction of 25–35% and a speckled appearance to the myocardium, suggestive of cardiac amyloidosis.

He remained well until August 2003, when he was admitted following a collapse at home. His dyspnoea had worsened over the preceding four weeks, despite regular use of bumetanide 2 mg and lisinopril 2.5 mg. Clinical examination revealed a petechial rash affecting the right arm and chest (Fig 1), bibasal pulmonary crepitations, a raised jugular venous pressure, and smooth hepatomegaly. Chest X-ray showed a left-sided pleural effusion, upper-lobe venous diversion and cardiomegaly. Plasma biochemistry showed mild renal impairment (urea 14.9 mmol/l, creatinine 133 µmol/l). He was treated with intravenous diuretics, once again to good effect.

A gingival biopsy confirmed the diagnosis of systemic amyloidosis, and subsequent urinalysis showed the presence of free lambda light chains,

Key Points

Cardiac involvement in amyloidosis is common and may be the first manifestation of systemic disease

The diagnosis of cardiac involvement in systemic amyloidosis normally can be made with a combination of imaging and biochemical modalities; myocardial biopsy is rarely necessary

The management of amyloid-related heart failure and rhythm disturbances is similar to that of non-amyloid cardiac disease, although patients may respond more sensitively, or even adversely, to some drug groups

Chemotherapy can have promising results in patients who have sufficient life expectancy to show a response, and organ transplantation may be of benefit in selected groups

The overall prognosis at this time remains poor

identifying the condition as primary (AL) amyloidosis. A bone-marrow trephine and aspirate showed no evidence of overt myeloma, although a paraprotein was detected in the blood.

During the course of his stay, he complained of symptoms consistent with bilateral carpal tunnel syndrome, a further reflection of systemic amyloid deposition. The potential for chemotherapy was discussed between renal physicians, haematologists and cardiologists. It was felt that he was unlikely to benefit in view of the severity of his cardiac disease. He was discharged after symptom relief had been achieved.

In September 2003, he re-presented with severe biventricular failure. Attempts at diuresis were hindered by severe hypotension. Several days later, he suffered a cardiac arrest, from which he was unable to be resuscitated. The cause of death was ascribed to primary (AL) amyloidosis with cardiac involvement.

Case study 2

A 46-year-old woman with no significant past medical history presented to Wythenshawe Hospital in September 2002. At this time, she appeared to have suffered a seizure at home. Although the nature of the collapse was not ascertained (computed tomography (CT) head and electroencephalogram (EEG) were normal), it was noted that she had severe cardiomegaly on a chest X-ray. She was discharged with plans for an outpatient echocardiogram and ambulatory ECG monitoring. Although no arrhythmias were recorded during Holter monitoring, the patient recorded in her observation diary dyspnoea on climbing stairs. The planned echocardiogram was preceded by an acute deterioration in her condition in October, requiring emergency admission.

At this time, she was acutely confused, dyspnoeic and jaundiced. Physical examination revealed hypotension (blood pressure 85/40 mmHg), jaundice, hepatomegaly and ascites. A chest X-ray showed cardiomegaly but clear lung fields. The ECG on admission revealed left bundle branch block. An ultrasound scan of the abdomen demonstrated ascites, a large right pleural effusion and an enlarged liver. A subsequent echocardiogram showed severely impaired left and right ventricles, with an estimated left ventricular ejection fraction of 10%. Gross tricuspid regurgitation was the only valvular abnormality of note.

Shortly after admission, she suffered an asystolic cardiac arrest and was transferred to the intensive care unit for mechanical ventilation. An intra-aortic balloon pump was inserted, dobutamine was commenced and intravenous diuretic therapy was instigated.

The following day, three toes on her left foot had turned black. The pedal pulses remained palpable, and an embolic aetiology was suspected. The possibility of a systemic vasculitis or viral hepatitis was excluded with negative viral and autoantibody screens. A repeat echocardiogram showed a severe global reduction in cardiac function, symmetrical hypertrophy of the ventricular walls and an interventricular septum thickness of 2 cm. There was also evidence of thrombus within the left ventricle.

The diagnosis of primary (AL) amyloidosis was confirmed by gingival biopsy and urinalysis. In the meantime, the embolic phenomena continued despite anticoagulation, and the patient's right foot was thought by the vascular surgical team to be non-viable. She died on the eighth day following admission. Postmortem examination revealed systemic amyloidosis with cardiac involvement, in addition to embolic disease in the peripheral and pulmonary circulations.

Discussion

The amyloidoses are a heterogeneous group of disorders that can present with either local or systemic disease. The feature common to all types is the deposition of insoluble fibrillar proteins in the extracellular space. The three diseases of most interest to the cardiologist are primary (AL) amyloidosis, the most common variant (affecting eight per million people per year¹), familial amyloid polyneuropathy (FAP) and senile cardiac amyloidosis. The remaining types of amyloidosis, including reactive (AA) amyloidosis, a common sequel of chronic infection or inflammation, are less likely to cause cardiac involvement.²

In primary (AL) amyloidosis, amyloid protein is formed by the deposition of immunoglobulin light chains. These patients have plasma cell dyscrasias that predispose them to monoclonal antibody production, detectable either in the serum or in



Fig 1. The patient in Case study 1 presented with this petechial rash, which can be a feature of systemic amyloidosis.

the urine. In the 10% of patients who display no detectable monoclonal antibodies, bone-marrow biopsy may reveal clonal dominance of plasma cells.

In the autosomal dominant inherited form of amyloidosis – FAP – the precursor for amyloid deposition is an abnormal variant of the protein transthyretin (TTR), produced within the liver. FAP is diagnosed through a combination of family history and isoelectric focusing of the serum in affected patients, which delineates the wild and variant forms of TTR.³ Senile cardiac amyloidosis is a common, though frequently underdiagnosed, condition in which small amounts of normal TTR protein are deposited in the heart with age.⁴ A post-mortem study of 244 unselected patients over the age of 60 years demonstrated such pathology in 49.6%.⁵ The clinical features are identical to those of AL amyloidosis, although the management and prognosis are radically different.

Clinical features

Systemic amyloidosis may present with a variety of signs, including peripheral oedema, hepatomegaly, postural hypotension, purpura, peripheral neuropathy and macroglossia. The nature of cardiac involvement in amyloidosis varies according to the underlying cause. Conductive tissue disease, particularly tachyarrhythmias, predominates in FAP, whereas congestive cardiac failure, with predominant diastolic dysfunction, prevails in AL amyloidosis.³ Senile amyloidosis is associated with both atrial fibrillation and congestive cardiac failure.⁶ Cardiac function is compromised by a combination of amyloid infiltration of heart tissues and a direct toxic effect of circulating light chains on the myocardium.⁷ Myocardial ischaemia is rare but, when present, is normally due to microvascular changes that are imperceptible on coronary angiography.⁸

One-quarter of patients with AL amyloidosis demonstrate autonomic neuropathy,⁹ of which postural hypotension is the most common manifestation. Patients in the early stages of the disease may rely on spontaneous hyperventilation to increase venous return and, hence, maintain cardiac output and systemic arterial pressure.¹⁰

Diagnosis of cardiac involvement

The diagnosis of cardiac amyloidosis is made through a demonstration of systemic amyloid deposition and characteristic findings on ECG and echocardiography (consistent with all types of amyloid).¹¹ The standard methods for demonstrating amyloid deposition include rectal, gingival and abdominal fat biopsies, where staining with Congo red produces the characteristic green birefringence under cross-polarised light (Fig 2). Endomyocardial biopsy itself is not indicated when the above criteria are met and a classification of the systemic amyloidosis is possible. However, if no plasma cell dyscrasia can be detected and there is no pertinent family history to suggest FAP, then it is essential to obtain myocardial specimens in order to exclude the relatively benign senile cardiac amyloidosis before embarking on potentially harmful therapeutic strategies.

Electrocardiographic features

The ECG features of cardiac amyloidosis include:^{3,12}

- low ECG voltages (< 0.5 mV mean QRS in leads I, II, III, aVL and aVF)
- pseudo-infarction pattern: QS waves in anteroseptal and/or inferior leads
- abnormal axis deviation
- ventricular and supraventricular arrhythmias (incidence no different between amyloid groups).

The sensitivity of these findings in all types of cardiac amyloidosis ranges between 80% and 100%,^{12,13} with all AL patients and 95% of FAP patients showing one or more of these abnormalities. ST segment depression has also been noted in these groups but appears to correlate with coronary artery amyloid deposition only in those patients describing chest pain. A further feature of AL amyloidosis is an inverse relationship between cardiac mass and ECG voltage, arising from the replacement of functioning myocardial cells with amyloid protein.¹⁴ This ‘low voltage, high mass’ characteristic can be useful in order to distinguish cardiac amyloidosis from pericardial disease (low voltage, low mass) and aortic valve disease (high voltage, high mass).¹⁵

Echocardiographic features

The echocardiographic features of cardiac amyloidosis include (Fig 3):

- increased right and left ventricular wall thickness
- increased myocardial echogenicity (‘granular sparkling’) – sensitivity 45%, but also found in Pompe’s disease and hypertrophic cardiomyopathy (HCM)
- valve thickening
- pericardial effusion
- thickening of interatrial septum
- atrial and ventricular thrombi.

There can be echocardiographic similarities between cardiac amyloidosis and HCM. Indeed, this is one of the few situations in which endomyocardial biopsy may become necessary in order to establish a diagnosis.¹⁶ Both left and right ventricular hypertrophy may occur in HCM, the latter representing either severe primary disease or a secondary response to pulmonary hypertension. However, in contrast to HCM, patients with cardiac amyloidosis and echocardiographic left ventricle (LV) wall thickening generally will not show ECG features of left ventricular hypertrophy. It has also been noted that patients with HCM have an interatrial septum/right atrial posterior wall thickness of less than 6 mm,¹³ whereas in amyloidosis diffuse cardiac involvement may lead to greater wall thickness.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) can improve the differentiation between amyloidosis and HCM, as the signal intensity of myocardium increases in HCM but decreases in amyloidosis. A

comparison of the myocardial signal intensity with that of skeletal muscle, which is unaffected by either condition, can improve sensitivity further.¹³

Biochemical markers

Radiolabelled serum amyloid P (SAP), a normal plasma protein that binds reversibly to amyloid, has been used for the detection of systemic amyloid deposits using gamma-camera technology.¹⁷ Unfortunately, this method produces poor views of the heart due to cardiac mobility, chest-wall attenuation and ventricular pooling of the tracer.¹⁸ Its main role is therefore limited to the preoperative assessment of extracardiac amyloid load in patients under consideration for cardiac transplantation.

Serum troponin levels are of little value in amyloidosis, as raised levels are found in most patients with cardiac involvement and are not related directly to coronary anatomy or haemodynamics.¹⁹

Prognostic indicators

In primary amyloidosis, a combination of LV wall thickness greater than 15 mm (an indirect assessment of diastolic function) and fractional shortening less than 20% (reflecting impaired systolic function) is associated with a median survival of 4 months.²⁰ The effect of ventricular hypertrophy on cavity size in amyloidosis differs between ventricles, with the left ventricular chamber reducing in size and the right ventricular chamber increasing secondary to high left atrial pressures and pulmonary vasculature involvement. Right ventricular dilation is regarded as evidence of increased disease severity in primary amyloidosis. There is, however, doubt as to the prognostic value of echocardiography in patients with FAP disease.

Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) has been shown to be valuable in the assessment of cardiac involvement in amyloidosis, with serum levels greater than 152 pmol/l demonstrating 93% sensitivity and 90% specificity for the detection of significant cardiac involvement in AL amyloidosis patients.²¹ The same study also demonstrated NT-proBNP to be the single most powerful prognostic factor in AL amyloidosis, with raised levels even detecting hitherto unapparent cardiac involvement.

Management

There is little firm evidence regarding the most appropriate way to manage patients with cardiac amyloidosis, but the decision depends on the nature of the underlying

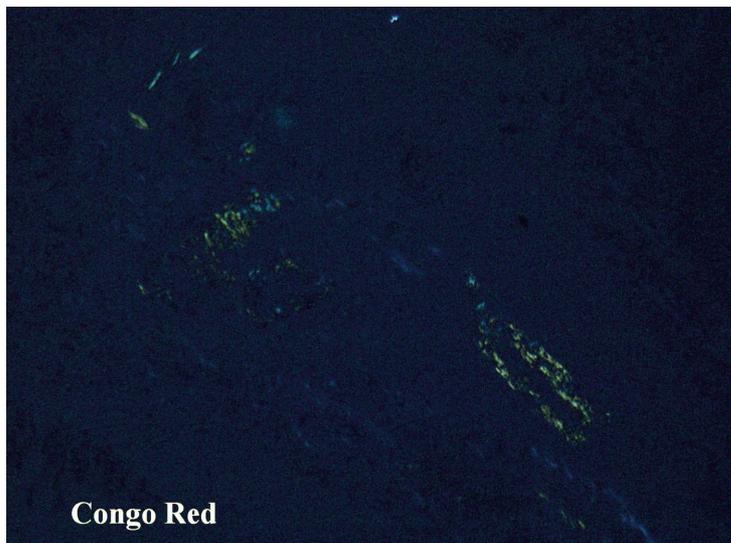


Fig 2. Amyloid deposition in a small-bowel specimen. Note the characteristic green birefringence of the amyloid fibrils when stained with Congo red and viewed under cross-polarising light.

disease, its cardiac manifestations and the extent of concomitant extracardiac disease.

The tendency towards low blood pressure in cardiac amyloidosis often creates difficulties, as the need for diuresis to treat symptomatic congestion must be balanced against the consequent symptomatic hypotension. Neither midodrine nor fludrocortisone have useful positive effect, but there have been

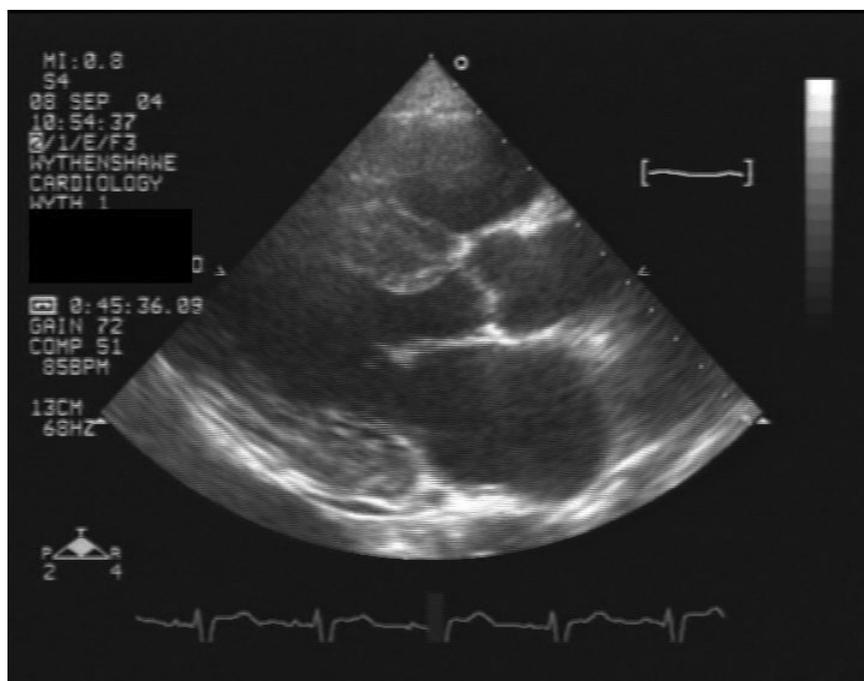


Fig 3. Transthoracic echocardiogram, showing features of cardiac amyloidosis. The left ventricle is hypertrophied, with a reflective myocardial appearance. There is thickening of the aortic valve and the tips of the mitral leaflets. The left atrium is enlarged, and a small pericardial effusion is seen posteriorly.

isolated reports of a response to subcutaneous erythropoietin, potentially due to mechanisms other than raised circulating haemoglobin levels.²²

Conduction disturbances are treated with pacing or antiarrhythmic agents where appropriate, although digoxin, verapamil and nifedipine should be avoided as they bind avidly to cardiac amyloid, producing unpredictable pharmacokinetics affecting the magnitude and duration of their action.²³ Patients demonstrating atrial or ventricular thrombus on echocardiography should also be anticoagulated. Aside from these recommendations, the management of cardiac failure in amyloidosis does not differ greatly from that in non-amyloid states, with diuresis being the central aim.

Chemotherapy

Primary (AL) amyloidosis, through its plasma-cell derivation, is treated with chemotherapy or stem-cell transplantation. Melphalan and prednisolone have proven benefit from randomised controlled trials,²⁴ although a median period of treatment of 1 year is needed for a clinical response. This is difficult to achieve in patients presenting with cardiac failure, where the average survival is less than 6 months.²⁵ NT-proBNP levels are a sensitive measure of the haematological response to chemotherapy, with up to 90% of patients showing some improvement, despite echocardiographic appearances remaining unchanged in 71% of such patients.

There is no role for chemotherapy in the management of senile cardiac amyloidosis, where the underlying problem is excessive deposition of normal TTR protein rather than a plasma cell dyscrasia. The management of this condition is directed at relieving its clinical features rather than attempting to halt the underlying process. The relatively benign nature of this condition is further reflected by a survival rate of 60 months following diagnosis compared with less than 6 months in AL amyloidosis.⁶

Stem-cell transplantation

Stem-cell transplantation can produce dramatic results in carefully selected AL amyloidosis groups, although generally this refers to patients without cardiac involvement in the first instance. Survival rates at 100 days approach 81% in patients with involvement of one or two organs but decrease to 33% in those with more widespread disease.¹ Patients presenting with cardiac failure, syncope, pleural effusions or a history of arrhythmias have a corresponding mortality of 100% when treated in this way.¹ Cardiac disease is undoubtedly an adverse prognostic factor for stem-cell therapy,²⁶ and some might regard it as an exclusion criterion in itself.

Organ transplantation

The familial form of amyloidosis (FAP), which has a better untreated prognosis than AL amyloidosis,²⁷ can be managed successfully through liver transplantation, with the aim of

removing the source of the abnormal TTR protein. A report of two such patients in Sweden has shown that TTR can be removed completely from the blood, and disease progression halted, by this approach.²⁸

The issue of cardiac transplantation in amyloidosis has proved very contentious, with most transplant teams expressing concerns regarding the effects of amyloid deposition at extracardiac sites and the inevitable recurrence of amyloid in the grafted organ.²⁹

The possibility of curative cardiac transplantation exists genuinely only in patents where there is a chance of halting the underlying amyloid deposition. In AL amyloidosis, this normally entails the use of chemotherapy, which can itself contribute to cardiac damage.³⁰ A few patients have undergone cardiac transplantation before stem-cell therapy with good results,³¹ but further studies are needed in this area. The situation is more encouraging in patients with FAP amyloidosis, where combined heart and liver transplantation appears promising.

Some observers have suggested that transplantation can act as a palliative measure, with survival rates in selected post-transplant patients reaching 60% in the first two years and 30% at five years. These figures compare favourably with those of patients with untreated cardiac AL amyloidosis, whose survival is 45% at one year, 22% at two years and 10% at five years.³² Isolated case reports have even described patients with AL amyloidosis living up to 10 years following the procedure.³³ The use of transplantation for palliation, however, will remain difficult to justify as long as donor hearts remain in short supply.

Future options

Future therapeutic options may include 4'-iodo-4'-deoxydoxorubicin, a promoter of amyloid resorption, although its role is yet to be clarified.³⁴ Similarly, the development of a drug that inhibits the binding of serum amyloid protein (SAP) to amyloid fibrils and facilitates SAP breakdown in the liver may hold promise following further trials.³⁵

Summary

As demonstrated by our two introductory case studies, the outlook for patients with primary (AL) cardiac amyloidosis remains poor. It remains the leading cause of death in patients suffering from systemic amyloidosis, and few effective methods are available to halt an inexorable decline. The outlook in FAP is better due to its unique pathophysiology, and early recognition of this condition can lead to a good outcome, particularly with liver transplantation. Senile cardiac amyloidosis, meanwhile, is a common and frequently underdiagnosed condition that has a relatively good prognosis with symptomatic therapy alone.

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