CASE REPORT

Life-saving implantable cardioverter defibrillator therapy in cardiac AL amyloidosis

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SUMMARY

Cardiac involvement is the main determinant of prognosis in systemic monoclonal immunoglobulin light chain (AL) amyloidosis. Ventricular arrhythmias and sudden cardiac death are not uncommon. The electrical events that precede sudden death, and their potential to be treated effectively, remain undefined. There are no European guidelines for the use of implantable cardioverter defibrillator (ICD) in amyloidosis. ICDs in general are not usually offered to patients with a life expectancy of less than 1 year. We describe a patient who presented with cardiac AL amyloidosis who underwent prophylactic ICD implantation for the prevention of sudden cardiac death during treatment with chemotherapy, in whom life-threatening ventricular arrhythmia was successfully terminated over a 3-year period.

BACKGROUND

The systemic amyloidoses are a group of rare multi-system disorders caused by the misfolding, aggregation and deposition of certain proteins in fibrillary form. Patients can present to almost any medical or surgical specialty depending on the organs affected. Cardiac involvement is common in monoclonal immunoglobulin light chain (AL) amyloidosis, the most frequently encountered systemic type, and confers a very poor prognosis. Median survival of patients with markedly elevated serum cardiac biomarkers is less than 1 year, and as little as 3.5 months in a defined subgroup of such patients. Data guiding clinicians about appropriate use of implantable cardioverter defibrillator (ICD) in cardiac amyloidosis are scarce, and the few small retrospective series and reviews in the medical literature have discouraged use of ICD implantation in this group of patients; no randomised-controlled trials of ICD have been performed. We report a well-characterised and comprehensively followed up patient with cardiac AL amyloidosis in whom ICD implantation was life-saving and enabled her to undergo effective chemotherapy for her underlying plasma cell disorder, encouraging the potential merits of this approach to be revisited in a prospective systematic manner.

CASE PRESENTATION

A 45-year-old Caucasian woman was found to have an abnormal ECG as part of a preassessment work-up for varicose vein surgery. On direct enquiry she reported a 2-year history of progressive dyspnoea, palpitations but no syncope and abdominal discomfort. Dyspnoea initially improved markedly after diuretic treatment. At initial assessment, she was in New York Heart Association (NYHA) class II and

reported dyspnoea on exertion although had a reasonable exercise tolerance of 0.5–1 mile including slight inclines. There was no medical or family history of note. She had four children who were well. Social history was negative for smoking and alcohol. Blood pressure (BP) was 111/68 with no postural fall. Physical examination revealed normal heart sounds with a faint pansystolic murmur, clear chest on auscultation of the lungs, a 3 cm non-tender palpable liver edge and no peripheral oedema.

INVESTIGATIONS

Twelve lead ECG ([figure 1](#)) demonstrated sinus rhythm with normal PR interval and QRS duration, poor R wave progression in chest leads, with Q waves in I and aVL and diffuse repolarisation abnormalities. QRS complexes were of a normal amplitude. Transthoracic echocardiography revealed mild biventricular increased wall thickness with a concentric pattern of thickening of the left ventricle (LV; 1.5 cm septum and posterior walls in diastole). LV ejection fraction (LVEF) was mildly impaired (EF 50%), with mildly impaired longitudinal systolic function, diastolic dysfunction with a restrictive filling pattern on Doppler assessment and an estimated pulmonary artery systolic pressure of 63 mm Hg. There was evidence of mild-to-moderate mitral regurgitation. The patient underwent cardiac MRI ([figure 2](#)) which showed a late gadolinium pattern of enhancement typical of cardiac amyloidosis and confirmed the other structural abnormalities found by echocardiography.

Endomyocardial biopsy was performed locally to attain a histological diagnosis and exclude other causes of hypertrophic cardiomyopathy. This revealed amorphous proteinaceous material which showed apple-green birefringence under cross-polarised light after staining with Congo red, the diagnostic hallmark of amyloid. This finding prompted specialist referral.

Blood tests showed elevated λ -free light chains of 344 mg/L with a κ : λ ratio of 0.02, N-terminal pro-brain natriuretic peptide (NT-ProBNP) 5649 ng/L, cardiac Trop T 0.03 ng/mL, and normal renal function with CrCl of 90 mL/min and estimated glomerular filtration rate (eGFR) of 70 mL/min. Urinalysis and 24 h urine collection confirmed the absence of significant proteinuria.

The patient underwent bone marrow aspirate and trephine which showed 30% plasma cells. ^{123}I -serum amyloid P component scintigraphy did not reveal amyloid deposits at other visceral sites.

A complete histological review of endomyocardial biopsy samples was undertaken including

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Figure 1 Twelve lead ECG demonstrating sinus rhythm with normal PR interval and QRS duration, poor R wave progression in chest leads, with Q waves in I and aVL and diffuse repolarisation abnormalities. QRS complexes are of a normal amplitude.

immunospecific staining of the endomyocardial biopsy with monospecific antibodies to λ light chains, and confirmed this to be cardiac AL amyloidosis of the λ subtype.

DIFFERENTIAL DIAGNOSIS

The clinical and histological findings provided a definitive diagnosis of systemic AL amyloidosis with dominant cardiac involvement, complicating asymptomatic multiple myeloma.

TREATMENT

Combination chemotherapy in the form of cyclophosphamide, thalidomide and dexamethasone (CTD) was started 3 weeks

after diagnosis. During the second week of treatment, the patient experienced a syncopal episode associated with chest pain and palpitations, and was admitted to hospital. Inpatient cardiac monitoring revealed atrial tachycardia during an episode of palpitations and dizziness. She was preferentially started on oral amiodarone rather than a β -blocker in view of a low systolic BP, monitored for a further period and discharged home after up-titration of diuretic therapy for fluid retention which developed after starting chemotherapy.

The patient was readmitted 3 days later with a second episode of syncope and palpitations. A CT pulmonary angiogram excluded pulmonary embolism, and further inpatient cardiac

Figure 2 Top: diastolic frame cines of three long-axis views showing moderate left ventricular hypertrophy of the left ventricle. Note this is predominantly at the level of the interventricular septum. Bottom: late gadolinium enhancement (LGE) images in the same planes with phase sensitive inversion recovery reconstruction. There is evidence of LGE which is more pronounced at the level of the subendocardium that becomes transmural in many areas. The blood pool is dark, which does not frequently occur in other conditions.

monitoring showed one salvo (4 beats) of non-sustained ventricular tachycardia (NSVT) associated with palpitations but no presyncope or syncope. No postural hypotension could be demonstrated. Coronary angiography demonstrated normal, unobstructed coronary arteries and right heart cardiac catheterisation excluded the presence of significantly elevated pressures suggestive of pulmonary hypertension. Chemotherapy with CTD was discontinued and an alternative combination of cyclophosphamide, bortezomib and dexamethasone started.

Thirteen days after starting this treatment, the patient was readmitted following a third syncopal episode associated with chest pain and progressive dyspnoea. Inpatient cardiac monitoring showed a brief episode (11 beats) of asymptomatic broad complex tachycardia compatible with NSVT. Although no definite causal relationship could be demonstrated with certainty, in view of repeated admissions with syncope and NSVT, urgent implantation of a prophylactic dual chamber ICD was undertaken to prevent sudden cardiac death.

The procedure was uncomplicated, successfully tested with internal defibrillation at a single shock of 26 J after ventricular fibrillation (VF) induction and the patient resumed planned chemotherapy. In view of the development of deranged liver function tests over this period, amiodarone was discontinued and a β -blocker was started. She completed two cycles of chemotherapy to a complete haematological response, followed by a third cycle of reduced dose subcutaneous bortezomib monotherapy. Cyclophosphamide and dexamethasone were discontinued in the third cycle in view of fluid retention and light-headedness noted at dosing with these treatments.

OUTCOME AND FOLLOW-UP

Three weeks after completing chemotherapy, the patient experienced therapy from the ICD; antitachycardia pacing (ATP) for

VT followed by VF which was successfully terminated with single shock at 41 J (figure 3). ICD interrogation also revealed an episode of VT which was successfully terminated with ATP, and two other self-terminating episodes of non-sustained VT which the device correctly identified. The β -blocker dose was uptitrated following this event.

More than 3 years following ICD implantation, by which time there had been a considerable improvement in the patient's cardiac status and no further cardiac arrhythmia, she experienced a fourth syncopal episode at home. ICD interrogation on this occasion revealed that a single ventricular ectopic provoked ventricular flutter for which the device delivered ATP followed by a 41 J shock which successfully terminated the arrhythmia (figure 4). The patient remains well and in employment more than 4 years following initial diagnosis with ICD home monitoring and ongoing local cardiac and haematological follow-up.

DISCUSSION

The prognosis of systemic AL amyloidosis with dominant cardiac involvement is generally very poor. A significant proportion of patients die before or during the first 2–3 months of chemotherapy, the mainstay of treatment for systemic AL amyloidosis. For some patients with the poorest prognosis who do receive treatment, this can be complicated by toxicities which significantly reduce quality of life and fail to provide survival benefit. The availability of novel plasma cell therapeutic agents^{1 2} can improve haematological responses and hence impact survival. The Mayo group described a staging system in 2004³ which is widely used to stratify patients into groups based on cardiac biomarkers to give estimated median survival times. Recently the same group has demonstrated that the addition of involved serum-free light chain levels to the staging system can provide additional prognostic information.⁴ The

Figure 3 First implantable cardioverter defibrillator therapy: atrial (A) and ventricular (V) electrograms (EGM; top), farfield EGM, and channel marker (bottom) demonstrating ventricular tachycardia (ventricular rate > atrial rate, cycle length 245–255 detected in the ventricular fibrillation (VF) zone) onset after PVC (premature ventricular contraction) (not shown), treated with short burst antitachycardia pacing (8 beats) followed by VF appropriately detected and terminated (41 J shock).

Figure 4 Implantable cardioverter defibrillator therapy more than 2 years following implantation: atrial and ventricular electrograms (EGM; top), farfield EGM, and channel marker (bottom) demonstrating ventricular tachycardia or ventricular flutter (cycle length 255–280 detected in the ventricular fibrillation (VF) zone) onset after PVC (not shown), treated with short burst antitachycardia pacing (8 beats) followed by VF appropriately detected and terminated (41 J shock).

median survival of a patient presenting with laboratory markers as in our patient with stage 2 disease is 10.5 months according to the original Mayo staging system. Low systolic BP (<100 mm Hg) and very elevated NT-proBNP (>8500 ng/L) in stage 3 AL amyloidosis has been shown to identify patients with the very poorest outcomes.⁵

In cardiac AL amyloidosis, the mode of death is often progressive heart failure or sudden cardiac death, and the prevalence of ventricular arrhythmia is thought to be high.⁶ The benefit of ICD therapy in cardiac amyloidosis remains unclear and the data in patients with cardiac AL amyloidosis are limited. Individual case reports and case series show benefit in some patients and not others. A case series of 53 patients from the Mayo Clinic⁷ included 33 patients with cardiac AL amyloidosis who received an ICD; 25 patients for primary and 8 patients for secondary prevention of sudden death. Six of the 25 patients in whom the device was implanted for primary prevention received at least one appropriate shock during the median follow-up period of 23.25 months as did 6 of 8 patients in whom implantation was for secondary prevention; however, analysis of these data showed no survival benefit despite appropriate therapies being delivered. As the authors highlight, this may have in part been due to device implantation in more advanced cases (impaired LV systolic function and/or unexplained syncope) in this series.

Kristen *et al*⁸ reported on 19 patients with cardiac AL amyloidosis with unexplained syncope and or documented significant ventricular arrhythmia in whom primary prevention ICD was implanted. During a median follow-up of 536 days, only two patients with sustained VT were successfully treated by ICD therapies. One of these unfortunately died 2 weeks later due to electromechanical dissociation (EMD) but the other received repeated therapy for VT and VF during follow-up and did not experience arrhythmic events in the subsequent 30 months following complete remission of the plasma cell dyscrasia and the

start of amiodarone. The authors concluded that patients with cardiac amyloidosis predominantly died as a result of EMD and other diagnoses not amenable to ICD therapy. Finally, Varr *et al*⁹ reported on 15 patients with ICD implantation for cardiac AL amyloidosis, 11 patients for primary prevention and 4 for secondary prevention. Two patients with ICD implanted for primary prevention received ICD therapies. Both of these patients were in NYHA class 2 at the time of implantation with LVEF 51% and 60%. Of these, one patient was treated with successful ATP and defibrillation by the ICD and remained alive at 6 months follow-up. The other patient received defibrillation for VF but unfortunately this was unsuccessful. Three patients receiving defibrillators for secondary prevention experienced device therapy. Two of these patients were in NYHA 2 and one in NYHA class 3; EF 60% in two patients and 40% in one patient. All patients received successful therapy; two patients had meaningful long-term survival (19 and 18 months); one patient died at 6 weeks.

ICD implantation guidelines in general have evolved over time in light of information from experience and large clinical trials. Guidelines for patients with ischaemic heart disease place appropriate evidence-based importance on the degree of LV systolic function measured by LVEF, but not for other cardiac diseases such as hypertrophic cardiomyopathy and channelopathies, where traditional risk factors for sudden death are not helpful in determining risk. Until the recent 2013 American College of Cardiology guidelines on the appropriate use criteria for ICD,¹⁰ there were no guidelines for device implantation in cardiac amyloidosis. These guidelines, for the first time, make two specific comments related to patients with amyloidosis. They state that for patients with cardiac amyloidosis who have unexplained syncope and impaired cardiac function (EF ≤49%), and for patients with amyloidosis associated with heart failure and any LVEF, ICD ‘may be appropriate care’. It is highlighted that the category of ‘may be appropriate’ represents groups of

Learning points

- ▶ The prognosis of patients with systemic AL amyloidosis and elevated cardiac biomarkers is poor, but timely and tailored chemotherapy can result in excellent haematological responses.
- ▶ Symptoms suggestive of possible cardiac arrhythmia (syncope, presyncope particularly without postural hypotension, palpitations and even chest pain) should be extensively investigated to exclude significant ventricular arrhythmia and is best achieved through collaboration between haematologists and cardiologists.
- ▶ Implantable cardioverter defibrillator (ICD) implantation is not recommended in general for patients with a life expectancy of less than 1 year; however, general guidelines are unsuitable for patients with rare diseases where published literature can be scanty, and each case should be considered individually, particularly when potentially effective treatment is available.
- ▶ A low threshold for ICD implantation for all but the very poorest prognostic groups may improve the short-term and long-term survival in patients with systemic AL amyloidosis and cardiac involvement.
- ▶ ICD implantation in cardiac AL amyloidosis can prolong survival with a good quality of life in some patients and recent guidelines suggest that ICD implantation may be appropriate in this setting.

patients in whom there is a lack of sufficient data to inform the decision and highlights the importance of applying clinical judgement to these cases.

This is only the second individual case report¹¹ to our knowledge where successful therapy delivered by a standard ICD system implanted prophylactically in cardiac AL amyloidosis has occurred on more than one occasion, and the first in which therapy was separated by a prolonged period of time, resulting in a meaningful survival benefit. These examples support the role for prophylactic ICD implantation in the management of highly selected patients with cardiac AL amyloidosis. Examples from case series also support this in the secondary prevention setting. The patients most likely to derive benefit from ICD implantation are possibly those with a reasonable quality of life, likely to survive treatment for amyloidosis, and without the

worst prognostic features. Prospective studies are needed but in the interim, ICD implantation for patients with cardiac AL can be safely undertaken and should be considered on an individual case basis.

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