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Case Report

Progressive Reduction in Left Ventricular Mass on Serial Cardiac Magnetic Resonance Imaging in a 67-year-old Male Patient With AL-Amyloidosis

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This is a report of serial cardiac magnetic resonance (CMR) findings over 8 years in a 67-year-old male with amyloid light chain (AL)-amyloidosis. CMR at diagnosis showed 4-chamber involvement with a substantial increase in left ventricular (LV) mass. CyBor-D (cyclophosphamide, bortezomib, dexamethasone) treatment resulted in complete remission with full recovery of functional capacity, and CMR studies at 5 and 8 years show a progressive reduction in LV mass. To our knowledge, this study has the longest CMR follow-up in a patient with cardiac AL-amyloidosis and illustrates the potential for substantial regression of cardiac amyloid protein when prolonged disease remission is achieved.

A previously healthy male patient presented in March, 2014, at age 59 years, with an 18-month history of progressive exertional dyspnea, postural dizziness, and presyncope. An avid long-distance cyclist, he found it increasingly difficult to keep up with his peer group of riders. His past history was significant for longstanding achalasia with dysphagia. He also described new symptoms of diarrhea, occasionally bloody. Clinical examination revealed that his heart rate was 55 beats per minute, his blood pressure was 115/70 mm Hg, and he had a soft systolic ejection murmur. Other physical signs included dystrophic fingernails and periorbital ecchymosis. Electrocardiogram showed prominent QRS voltages with ST-T abnormalities consistent with ischemia or strain.

There was serial evidence of diminishing functional capacity with a decline in maximum workload achieved from 12.3 to 10.0 Mets on treadmill testing over a 10-month span. Coronary angiography in August 2013 revealed normal coronary vessels. Over this same 10-month period, serial echocardiogram showed progression in septal wall thickness from 12 to 14 mm, posterior wall thickness from 12 to 13 mm, and left atrial diameter from 46 to 55 mm.

Cardiac magnetic resonance (CMR) imaging in May, 2014 showed an LV ejection fraction of 49%, LV mass of 375 g (normal 108-184 g) with diffuse subendocardial LV late gadolinium enhancement (LGE), and difficulty in nulling the normal myocardium, characteristic for infiltrative cardiomyopathy including cardiac amyloidosis[1] (Fig. 1).

Serum protein electrophoresis showed diffuse gamma region elevation with suppression of IgA and IgM. Free—light chain measurements were abnormal, with free lambda of 214.5 mg/L, free kappa of 14.1 mg/L, and a kappa/lambda (K/L) ratio of 0.07. Troponin I and B-type natriuretic peptide (BNP) levels were elevated at 0.11 μg/L and 346.7 pg/L, respectively. Bone marrow aspirate showed abnormal lambda+ plasma cells, and biopsy showed marked bone remodelling, but amyloid was not detected.

The diagnosis of amyloidosis was ultimately confirmed from a biopsy of the transverse colon, which displayed apple-green birefringence to polarized light on Congo Red staining in focal areas of the submucosal vessels.

Treatment with 8 monthly courses of CyBor-D (cyclophosphamide, bortezomib, dexamethasone) was initiated in July 2014, with a complete response after 2 months, with a reduction in free lambda to 22.9 mg/L and free kappa to 10.8 mg/L, and normalization of the K/L ratio to 0.47. Troponin and BNP levels trended progressively down and had normalized at 0.0 μg/L and 93.8 pg/L, respectively, by the completion of chemotherapy.

Clinical Course

The patient remained in complete remission during follow-up and was able to maintain long-distance cycling activities between chemotherapy treatments and afterwards, regaining pre-illness levels of functional capacity at 17.2 Mets

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Novel Teaching Points

- The potential exists for meaningful reduction of amyloid protein in cardiac tissues over time in patients with AL-amyloidosis and complete remission.
- Regular exercise may play a role in cardiac amyloid regression, but this observation requires further study.

on treadmill testing in 2017 and 2019. He had 2 episodes of paroxysmal atrial fibrillation while cycling, in September 2017 and February 2018, prompting the initiation of apixaban and bisoprolol.

A follow-up CMR study was done, in July 2019 to guide decision-making regarding the need for ongoing anticoagulation, and in April 2022 at the patient's request. Comparative results of the 3 studies are shown in Table 1, with evidence of progressive reduction in LV mass and parallel improvement in other functional parameters including normalization of LV ejection fraction.

Qualitatively less myocardial LGE was seen on each of the successive studies, with improved ability to null the normal LV myocardium, most clearly visualized on the 2022 study (Fig. 1). Quantitative evaluation of the LGE using the 5−standard deviation method yielded the following results: 2014—12.7%; 2019—12.6%; and 2022—11.6%.

Factoring in the progressive reduction in LV mass, these percentages translate to a parallel reduction in the amount of LGE burden, consistent with reduced myocardial amyloid protein.

Discussion

Amyloid light chain (AL)-amyloidosis is one of the principal forms of systemic amyloidosis and is characterized by multi-system aggregation and deposition of misfolded monoclonal immunoglobulin light chains as insoluble amyloid fibrils thought to be resistant to proteolysis. Early diagnosis and initiation of chemotherapy targeted at rapid suppression of the clonal plasma cell dyscrasia is the cornerstone of treatment, along with supportive approaches to preserve end organ function. Advances such as the inclusion of bortezomib, and more recently daratumumab, in treatment protocols have been associated with improved survival, but the disease still carries significant mortality and morbidity.

Spontaneous regression of cardiac amyloid protein has been described in a case series of 31 patients with treated AL-amyloidosis who underwent serial CMR evaluation pre- and post-chemotherapy over a 4-year span.[2] Regression was

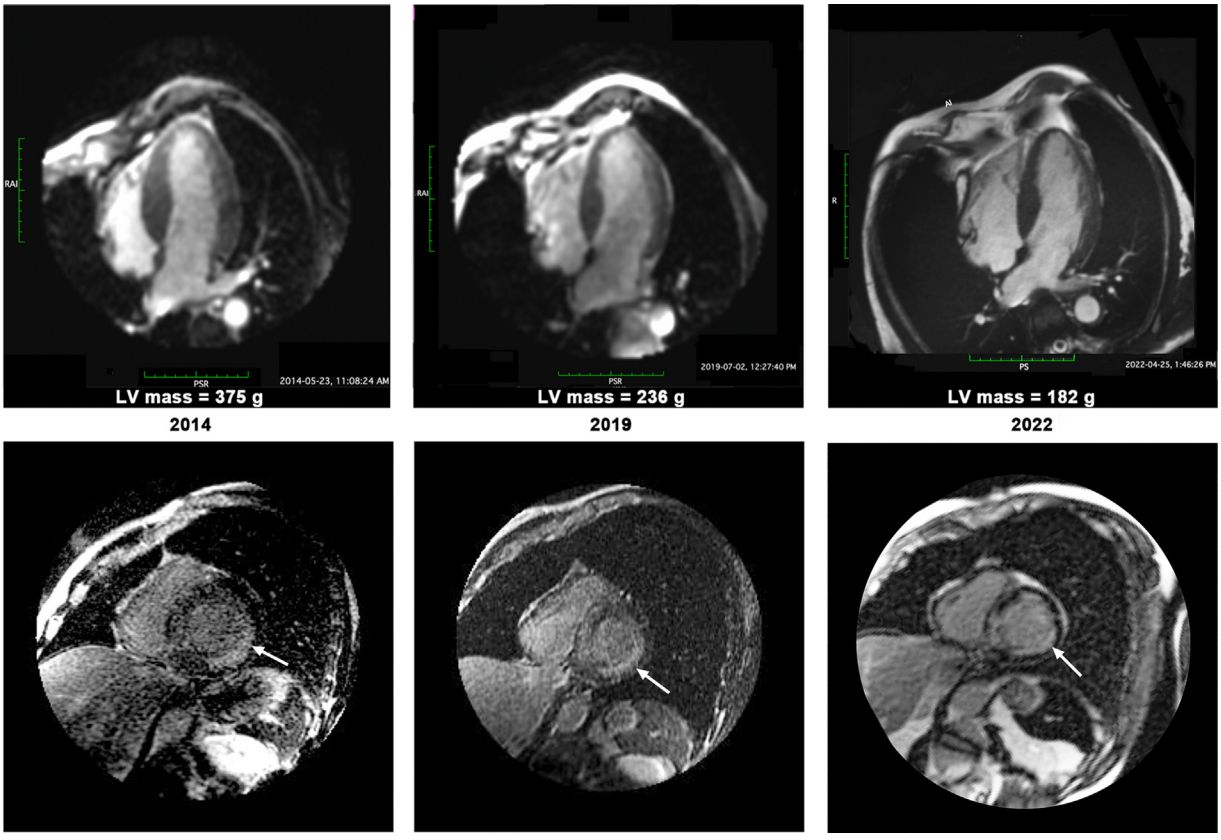

Figure 1. End diastolic frames (4-chamber cine) are shown in the **top row** for 2014, 2019, and 2022 studies, as indicated. Mid-ventricular short-axis frames showing the extent of late gadolinium enhancement (**arrows**) are shown in the **bottom row** for the respective studies. LV, left ventricular.

Table 1. Cardiac magnetic resonance parameters of cardiac structure and function, 2014–2022

Study date	LV mass, g	LV EDV, mL	LV ESV, mL	LV EF, %	LA area cm^2	RV EDV, mL	RV ESV, mL	RV EF, %	RA area, cm^2
May 23, 2014	375	296	153	48	38	217	110	49	25
July 2, 2019	238	217	95	56	28	230	123	47	18
April 25, 2022	182	204	77	62	28	218	97	56	24

EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; LV, left ventricular; RA, right atrial; RV, right ventricular.

defined as a fall of greater than 22% (equivalent to 2 standard deviations) in extracellular volume, and this extent of regression was noted in 13 of 31 patients. Evidence for regression was largely confined to patients with a complete or very good partial response to chemotherapy. Of those patients with "regression," lower LV mass was seen in 7 of 13, and improvement in LGE was seen in 5 of 13. Against this backdrop, a fall in LV mass of > 50% with a parallel fall in LGE over 8 years of follow-up in our patient is noteworthy.

Several factors merit consideration when determining the basis for a 50% decline in LV mass over 8 years. First, an active premorbid lifestyle may partially explain the higher LV mass seen on our patient's index 2014 CMR study, but it cannot account for subsequent declines in LV mass, as our patient's level of fitness, as objectively assessed by treadmill testing, was actually higher at the time of the follow-up CMR studies. Second, myocardial edema is known to be present in patients with AL-amyloidosis, particularly prior to initiation of chemotherapy.[3] Resolution of myocardial edema may have been a factor in the declining LV mass, but it is unlikely to account for a progressive 50% decline in mass over a span of 8 years, as was seen in our patient. Third, changes in loading conditions or body mass could affect LV mass, but they were not a factor in our patient. Last, the progressive and proportional fall in LV mass and quantitative LGE suggest that amyloid protein regression may be a more likely explanation.

Prior to his diagnosis, our patient's active lifestyle may have unmasked his disease at an earlier stage, while symptoms were still New York Heart Association functional class II and LV systolic function was only mildly impaired, and before more advanced incapacity and multiorgan involvement had become manifest. It is thus worth emphasizing the need for greater awareness of the ways that cardiac AL-amyloidosis may present, as its early recognition is paramount to achieving a good patient outcome. An early and complete response to chemotherapy has been associated with longer periods of remission and improved survival, and limited data show a correlation with cardiac amyloid regression.[2] Whether our patient's activity level had an impact on the particularly favourable cardiac remodeling seen on serial CMR is speculative and requires further study.

The accrual of amyloid protein in tissues is a product of the amount of circulating substrate (in the case of AL-amyloidosis, clonal light chain) and time. The extent of amyloid protein regression seen in our patient points to the potential for breakdown and resorption of these amyloid deposits during extended periods of complete remission, and challenges the commonly held belief that amyloid deposition is irreversible.

Ethics Statement

All of the findings in this publication have adhered to institutional ethical guidelines and standards.

Patient Consent

The authors confirm that patient consent forms have been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

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