

Removal of cardiac AL amyloid with positive remodelling of cardiomyocytes and of restrictive cardiomyopathy

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Abstract

Herein, we describe histological mobilization of light chain cardiac amyloid documented by sequential left ventricular endomyocardial biopsies. These findings were associated with positive remodelling of cardiomyocytes and of restrictive cardiomyopathy resulting from 14 courses of chemotherapy over 17 years of time. Histological and ultrastructural findings of light chain cardiac amyloid removal led to increase in cardiomyocyte dimension and electrocardiogram voltages, reduction of biventricular wall thickness with improvement of left ventricular diastolic function, and NYHA class shifting from III to I.

Keywords Cardiac AL amyloid; Remodelling; Restrictive cardiomyopathy

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Introduction

Cardiac amyloid (CA) is an infiltrative myocardial disease caused by interstitial deposition of beta fibrils,^{1,2} giving rise to a cardiomyopathy with restrictive phenotype. The generation of amyloidogenic proteins can have a genetic basis (e.g. mutation of transthyretin and apolipoprotein A1 and A2 genes) or be acquired [e.g. serum amyloid A, light chain (AL), and transthyretin amyloidosis]. If appropriately treated, AL amyloid can have a survival of up to 10 years³; however, the mechanisms (e.g. toxic L-chain suppression or amyloid removal) correlated to treatment-related clinical benefits are still hypothetical.

Case report

A 71-year-old lady with a history of bilateral carpal tunnel surgery was diagnosed with AL CA in 2004 and subsequently submitted to several courses of chemotherapy because of

monoclonal gammopathy-related AL-K CA and a number of plasma cells <10% at bone marrow biopsy. At the time of diagnosis, the patient suffered from recurrent episodes of abdominal pain, dyspnoea (NYHA Class III), and perimaleolar oedema; blood pressure was 110/70 mmHg, and there were no signs/symptoms of neuropathy. Blood tests showed increased levels of alkaline phosphatase (427 U/L n.v. <279), NT-proBNP 3188 ng/L (n.v. <334 ng/L), proteinuria 0.24 g/24 h, creatinemia 0.5 mg/dL. CA was confirmed via left ventricular (LV) endomyocardial biopsy with histological and ultrastructural evaluation, as well as immunohistochemistry for light chain; transthoracic echocardiography documented restrictive cardiomyopathy with enlarged left atrium, diffuse biventricular hypertrophy [18.2 mm maximal wall thickening (MWT) at interventricular septum], diastolic dysfunction with E/A ratio 2.45, preserved LV systolic function (LVEF 55%), and NYHA Class III. The patient was referred to a haematologist, who confirmed the diagnosis of AL amyloidosis [free circulating kappa light chain level: 233 mg/L (n.v. <19.4 mg/L)] with predominant hepatic and cardiac involvement. She was

started on melphalan (10 mg/die) and dexamethasone (20 mg/die). In 2005, following six courses of therapy, there was a remission of the haematologic disease and an improvement of cardiac function. Two years later (2007), a disease relapse was noted, which required four other courses of chemotherapy. In 2014, she was treated with cyclophosphamide, bortezomib, and dexamethasone (four courses) due to a new disease relapse. Cardiac function did not worsen with disease relapse; contrariwise, there was a progressive improvement of dyspnoea with NYHA class improving from III to I and serum NT-proBNP declining from 3188 to 480 pg/mL (n.v. <334 pg/mL).

In 2021, the patient experienced a flu-like syndrome with upper respiratory infection; she was subsequently admitted to the hospital presenting with symptoms suggestive of acute myocarditis, including palpitations and chest pain; baseline electrocardiogram documented intermittent phases of atrial fibrillation. The patient was re-evaluated with immunoelectrophoresis, echocardiogram, cardiac magnetic resonance, coronary angiography and LV endomyocardial biopsy. Invasive studies were performed because of chest pain and suspicious myocarditis. Serum AL-K monoclonal chain level had decreased from initial 233 to 18.2 mg/L (n.v. <19.4 mg/L). Follow-up electrocardiogram showed sinus rhythm at

Figure 1 Comparison between electrocardiogram and echo findings at baseline and after 17 years of immunosuppressive therapy. (A) Twelve leads ECG at baseline showing sinus tachycardia with diffuse low QRS voltages. (B) Follow-up 12 leads electrocardiogram with increased QRS voltages more evident in the peripheral leads. (C) Two-dimensional (2D) echocardiogram with restrictive trans-mitral flow pattern (E/A = 2.5). (D) After 17 years, diastolic function improved as demonstrated by *trans-mitral flow* velocity profile showing reversal of the E/A ratio (E/A = 0.5). (E) 2D echocardiographic four-chamber end-diastolic (left) and end-systolic (right) view at baseline showing increased thickness of the left ventricular (LV) wall (maximal wall thickness = 18.2 mm), with reduced LV end-diastolic volume (48.5 mL) and preserved LV ejection fraction (55%). (F) 2D echocardiographic four-chamber end-diastolic (left) and end-systolic (right) view at 17-year follow-up showing reduction of wall thickness (14 mm) increase in LV end-diastolic volume (75 mL) and increase ejection fraction (60%).

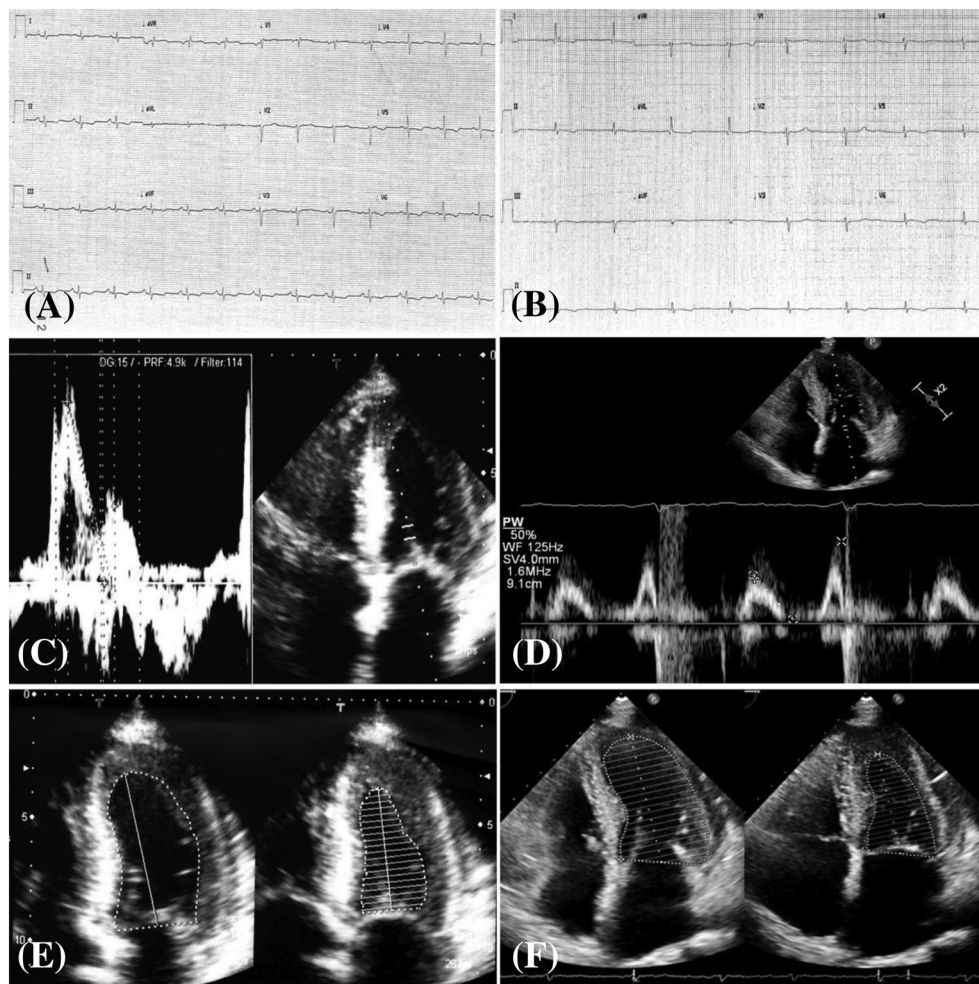
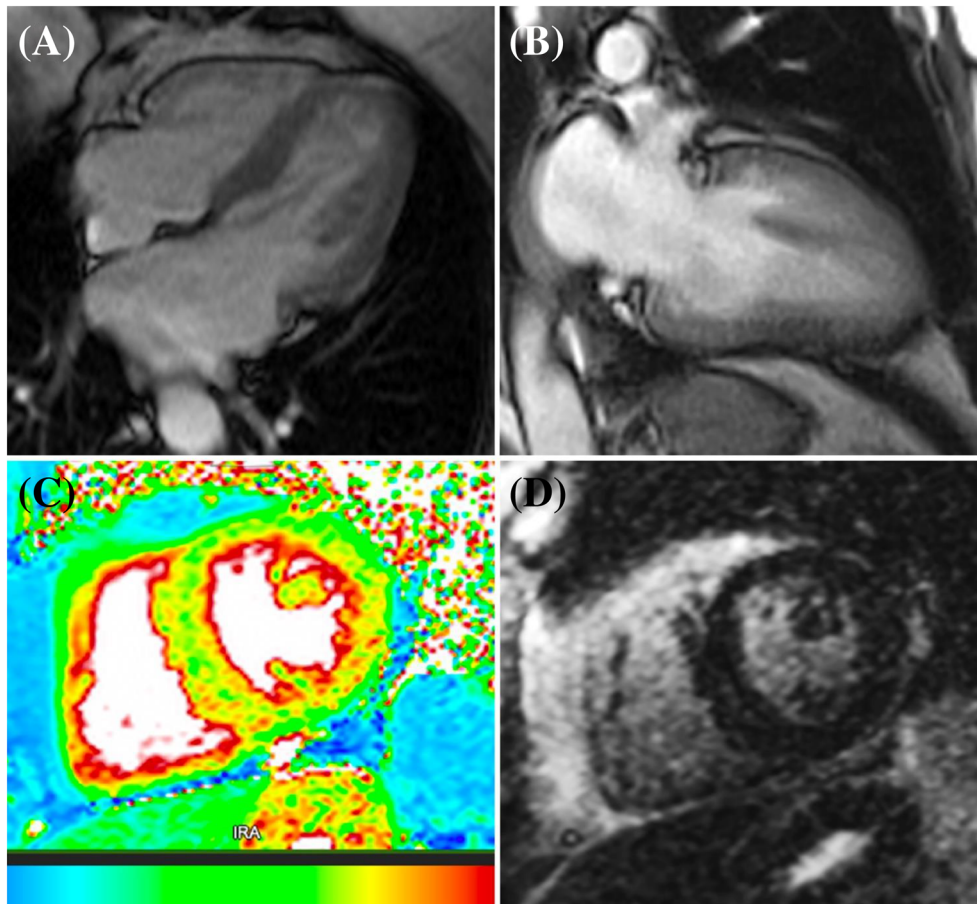


Figure 2 Cardiac magnetic resonance after 17 years from the diagnosis of cardiac AL amyloidosis. CMR revealed normal myocardial wall thickness on cineMR images acquired on horizontal (A) and vertical (B) long axes, with preserved systolic function. Mid-ventricular T1 map (C) show normal global native myocardial T1; no areas of enhancement or typical ‘zebra’ pattern were found on late gadolinium-enhanced images (D).



60 bts/min with evidence of increased QRS voltages compared with pre-treatment values. Echocardiogram showed cardiac wall thinning with reduction of MWT from 18.2 to 14 mm, smaller left atrial dimensions, and improved diastolic dysfunction (E/A ratio shifting from 2.45 to 0.5). LVEF remained normal (60%). Cardiac magnetic resonance confirmed normal myocardial wall thickness with preserved systolic function. Mid-ventricular T1 map showed normal global native myocardial T1 (952 ± 87 ms, normal range <990 ms); no areas of enhancement or typical ‘zebra’ pattern were found on late gadolinium-enhanced images (*Figures 1 and 2*).

Coronary angiography was normal. Unexpectedly, at histology and electron microscopy, cardiomyocytes were clearly hypertrophied compared with pre-treatment values (mean diameter 32.58 ± 5.82 vs. 14.17 ± 2.93 μ) and cleared of amyloid fibrils that were scanty in the interstitium and distant from cardiac cells (see *Figure 3*), suggesting a possible improvement of cell nutrition. Engulfed macrophages with amyloid fibrils (*Figure 3G*) were commonly observed. No acute myocarditis was detected.

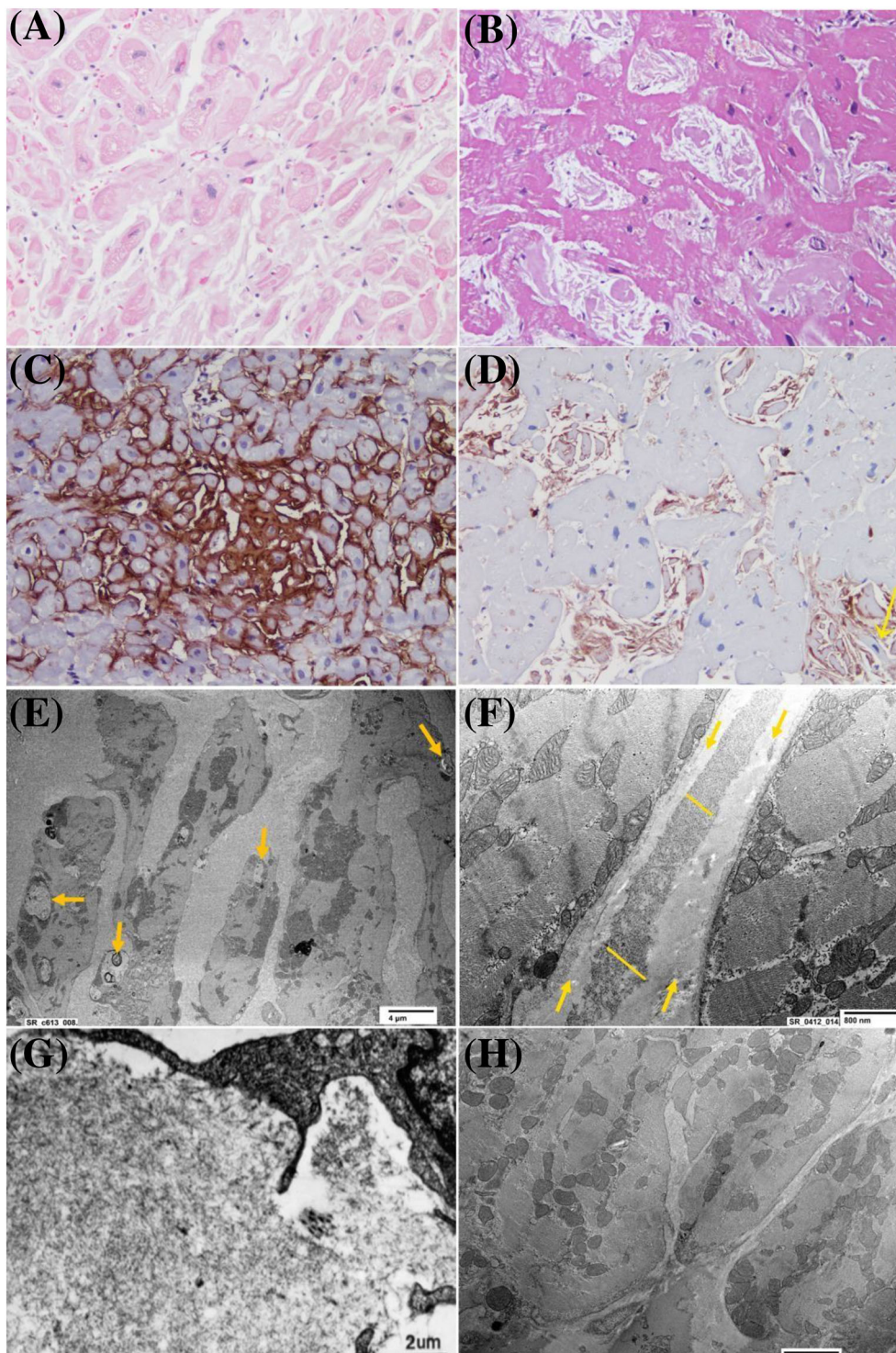
Following these investigations, the patient received a combination of anti-arrhythmic therapy including amiodarone 200 mg and bisoprolol 2.5 mg daily, which allowed maintenance of sinus rhythm and warfarin as anti-coagulation agent.

Discussion

CA due to monoclonal gammopathy is the most common cause of restrictive cardiomyopathy in human. If appropriately treated, this entity can allow a survival of up to 10 years.³ However, the mechanism involved is still unclear. Indeed, several pathways are hypothesized including suppression by therapy of toxic L-chain.

Our report documents for the first time a morphological removal of AL amyloid with positive histological (cardiomyocytes) and anatomical (cardiac chamber morphology and function) remodelling.

Figure 3 Histological, immunohistochemical, and ultrastructural evidence of AL-K CA being removed from myocardium with positive cardiomyocyte remodelling. (A and B) Hypotrophic cardiomyocytes surrounded by amyloid (A) becoming hypertrophied (B) after amyloid mobilization allowing cell nutrition (EE, magnification 160× for A and B). (C and D) Immunohistochemistry for AL-K amyloid denoting extensive CA deposition (C) that reduce remarkably (D) after immunosuppressive therapy (IHC, magnification 160× for C and D). (E) A large extracellular space filled by fibrillar amyloid. Hypotrophic cardiomyocytes show peripheral vesicles containing fibrillar and heterogeneous material (arrows). Disorganized sarcomeres and abnormal mitochondrial distribution are seen. (F) Constrained amyloid substance allows cardiomyocyte nutrition. (G) Interstitial macrophage engulfed with amyloid. (H) Recovered cardiomyocyte structure and components after treatment.



Specifically, after several courses of immunosuppression including melphalan and steroids because of a monoclonal gammopathy AL-K, left atrial dimensions, cardiac wall thickness, and E/A ratio reduced with concomitant improvement in NYHA class from III to I and decline of NT-proBNP level, biomarker of diastolic dysfunction. Immunoelectrophoresis for monoclonal gammopathy turned to be normal while cardiac magnetic resonance failed to recognize abnormal signals attributable to CA. The most striking evidence of CA mobilization came, however, from endomyocardial biopsy obtained at diagnosis and after 17 years of follow-up. The opportunity for a second endomyocardial biopsy raised by the evidence of normal coronary arteries at coronary angiography, presence of a normal valvular pattern, and the appearance of electric instability following a flu-like syndrome suggesting an acute myocarditis. Indeed, it has been shown atrial electrical instability can be the first manifestation of an acute myocarditis, possibly involving also the ventricular cavity.⁴ On the other hand, recent scientific statements^{5,6} indicate the suspicion of acute myocarditis as a major indication to perform an endomyocardial biopsy. It can be argued that magnetic resonance was negative in that setting for acute myocarditis. Probably because of the presence of heart rate irregularity and motion artifacts together with a more focal myocardial inflammation.⁷

Endomyocardial biopsy findings documented clear cardiomyocyte hypertrophy, compared with previous cell hypo/atrophy, and amyloid fibrils reduced in amount and far away from myocyte's membrane. Regarding mechanism

of CA re-absorption, control of amyloidogenic source by immunosuppressive agents and degradation of amyloid fibrils by interstitial macrophages and autophagy of intracellularly internalized material appear to concur.

It may be argued that histological findings can be limited by sampling of endomyocardial biopsy and do not necessarily represent the whole heart. Nevertheless, reduction of myocardial mass and improvement of diastolic function, as well as increase in QRS voltages, further supports our hypothesis that the observed morphologic changes would be a generalized phenomenon.

In conclusion, our features strongly suggest the possibility to remove CA and the option for the related cardiomyopathy to be potentially improved along with remission of AL gammopathy.

Conflict of interest

None.

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