

# Case report: Two sisters with light-chain cardiac amyloidosis, a mere coincidence?

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## Background

Light-chain amyloidosis has always been described as a sporadic disease caused by plasma cell dyscrasia. Cardiac amyloidosis refers to cardiac involvement with infiltration of amyloid fibrils in the myocardium. The degree of cardiac involvement is the greatest predictor of prognosis. To our knowledge, AL cardiac amyloidosis has only been reported once before in first-degree relatives.

## Case summary

In this report, we describe the unusual cases of two sisters with light-chain cardiac amyloidosis. The first patient underwent autologous stem cell transplantation and remained in remission for 10 years until the disease relapsed and she died of end-stage heart failure. The second patient was promptly started on a chemotherapy regimen but died shortly after her initial diagnosis due to rapid progression of cardiac dysfunction.

## Conclusion

Cardiac amyloidosis is a severe life-threatening condition which requires a multidisciplinary diagnostic and therapeutic approach. Based on this case report, a genetic cause for AL amyloidosis might be suspected or is this a purely coincidental finding? Counselling, screening, and follow-up of other family members are very challenging. As is often the case with rare diseases, many unsolved questions remain, representing important challenges for clinicians.

## Keywords

Cardiac amyloidosis • Light-chain amyloidosis • Familial • Case report

## ESC Curriculum

2.2 Echocardiography • 2.3 Cardiac magnetic resonance • 6.5 Cardiomyopathy

## Learning Points

- Light chain amyloidosis is a rare disease caused by plasma cell dyscrasia. Cardiac amyloidosis refers to cardiac involvement with infiltration of amyloid fibrils in the myocardium. The degree of cardiac involvement is the greatest predictor of prognosis.
- Sporadic reports of relatives affected by AL amyloidosis raise the possibility that a genetic predisposition may play a role in the development of the disease. This aspect deserves future research.
- Diagnosis, treatment, and follow-up of light chain amyloidosis require a multidisciplinary approach.

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## Introduction

A systemic amyloidosis is a group of diseases caused by the deposition of insoluble protein aggregates in different organ tissues, eventually leading to organ dysfunction.<sup>1</sup> Virtually any organ can be affected, including the heart, the kidneys, liver, gastro-intestinal tract, autonomic, or peripheral nervous system.<sup>2</sup> Cardiac amyloidosis refers to cardiac involvement with infiltration of amyloid fibrils in the myocardium. The degree of cardiac involvement is the greatest predictor of prognosis.

To our knowledge, AL cardiac amyloidosis has only been reported once before in first-degree relatives, namely in a father and his son.<sup>3</sup> In this report, we describe the unusual cases of two sisters with light-chain cardiac amyloidosis. This case raises very relevant questions for the patients and their family members. Is there a genetic cause and is screening necessary? As is often the case with very rare diseases, many unsolved questions remain.

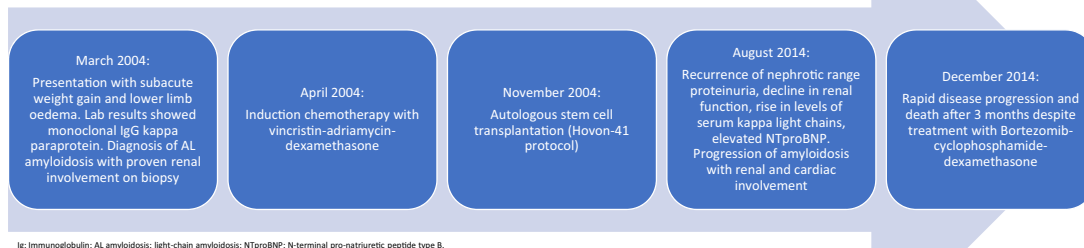
## Timeline

## Case presentation

### Case 1

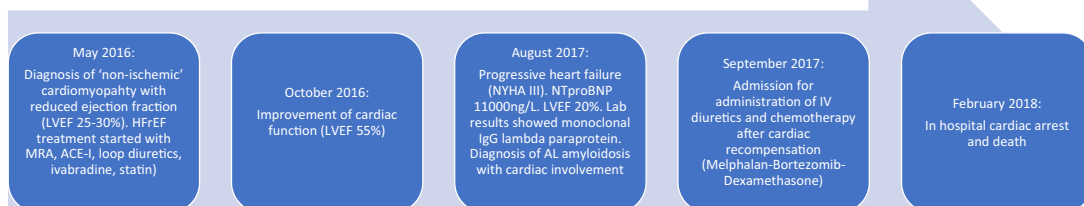
A previously healthy, 46-year old woman presented at our hospital in March 2004 with sub-acute weight gain (7 kg over a period of 6 months) and lower limb oedema. Clinical examination indicated normal heart rate and blood pressure and significant bimalleolar pitting oedema. Laboratory results showed normal renal function, normal calcium, normal haemoglobin, and blood cell count, normal glucose levels, but a remarkable hypoalbuminaemia (25 g/dL, normal range 35–52 g/L) and dyslipidaemia [total cholesterol 337 mg/dL (normally < 190 mg/dL), low-density lipoprotein-cholesterol 218 mg/dL (normally < 115 mg/dL), and triglycerides 260 mg/dL (normally < 180 mg/dL)]. Urine analysis revealed nephrotic range proteinuria (7.82 g/24 h, normal range < 0.15 g/24 u). Additional testing with protein electrophoresis and immunophenotyping revealed a monoclonal immunoglobulin (Ig) G kappa paraprotein (IgG 7.69 g/L, normal range 7.51–15.60 g/L) with the presence of IgG paraprotein and excess kappa light chains.

### Timeline Case 1



Ig: Immunoglobulin; AL amyloidosis: light-chain amyloidosis; NTproBNP: N-terminal pro-natriuretic peptide type B.

### Timeline Case 2



LVEF: left ventricular ejection fraction; HFREF: heart failure with reduced ejection fraction; MRA: mineralocorticoid antagonist; ACE-I: Angiotensin-converting enzyme inhibitor; NYHA: New York Heart Association; NTproBNP: N-terminal pro-natriuretic peptide type B; Ig: Immunoglobulin; AL amyloidosis: light-chain amyloidosis; IV: intravenous.

Renal biopsy was performed and revealed deposition of amorph eosinophilic material in the mesangium, mainly along with the capillary loops. Congo red staining was positive, but additional immunological staining for amyloid A and kappa/lambda light chains were negative. On bone marrow smear, a small monoclonal plasma cell population was found (IgG kappa light chains). Bone marrow biopsy revealed 5.7% of plasma cells (normally < 2.7%) staining positive for kappa light chains and in addition there was a deposition of amyloid in the small blood vessels. Chest and bone X-rays performed in search of osteolytic lesions were negative. An echocardiography revealed a structurally normal heart with normal systolic and diastolic function.

Based on these results, the tentative diagnosis of primary AL amyloidosis with proven renal involvement was confirmed. Induction chemotherapy with three cycles vincristine–adriamycin–dexamethasone was started, followed by stem cell collection, high-dose melphalan, and autologous stem cell transplantation 8 months after initial presentation, according to the Hovon-41 protocol.<sup>4</sup> Two months following transplantation, there were no detectable monoclonal fractions in blood or urine samples with gradual regression of the nephrotic syndrome.

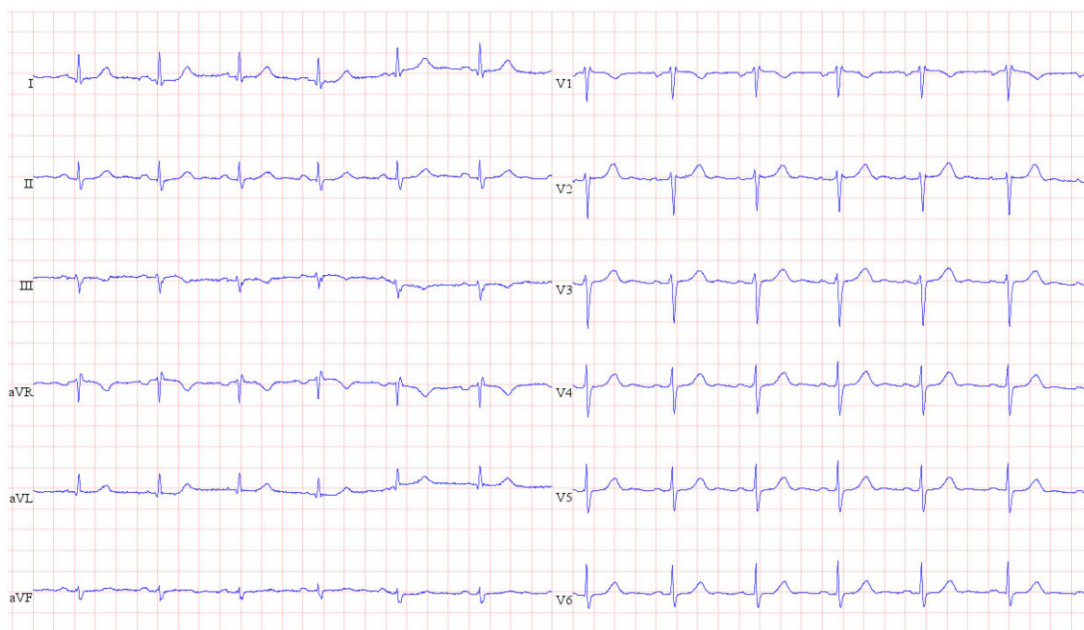
The patient remained in remission for almost 10 years until follow-up lab results showed a decline in renal function with recurrence of the nephrotic range proteinuria and a significant rise in levels of serum kappa light chains (111 mg/L, normal range 3.30–19.40 mg/L). Electrocardiogram recording is depicted in [Figure 1](#), showing relatively low voltages in peripheral leads. Echocardiography ([Figure 2](#); [Video 1](#)) now revealed light left ventricular (LV) hypertrophy [interventricular septum 1.2 cm (normal value < 0.9 cm); posterior wall 1.2 cm (normal value < 0.9 cm)] with preserved ejection fraction (normal value 54–74%). Furthermore, there was a significant rise in N-terminal pro-natriuretic peptide type B (NTproBNP) (2531 ng/L,

normally < 125 ng/L) and cardiac enzymes [high sensitivity cardiac troponin (hs-cTnt) 0.022 µg/L, normal value < 0.014 µg/L]. Considering her medical history, this was highly suggestive of the progression of amyloidosis with both renal and cardiac involvement. According to the Mayo classification,<sup>5</sup> she was found to be in Stage II. Chemotherapy regimen with bortezomib–cyclophosphamide–dexamethasone was started, unfortunately with very limited effect on the disease. Due to rapid disease progression, the patient died 4 months later.

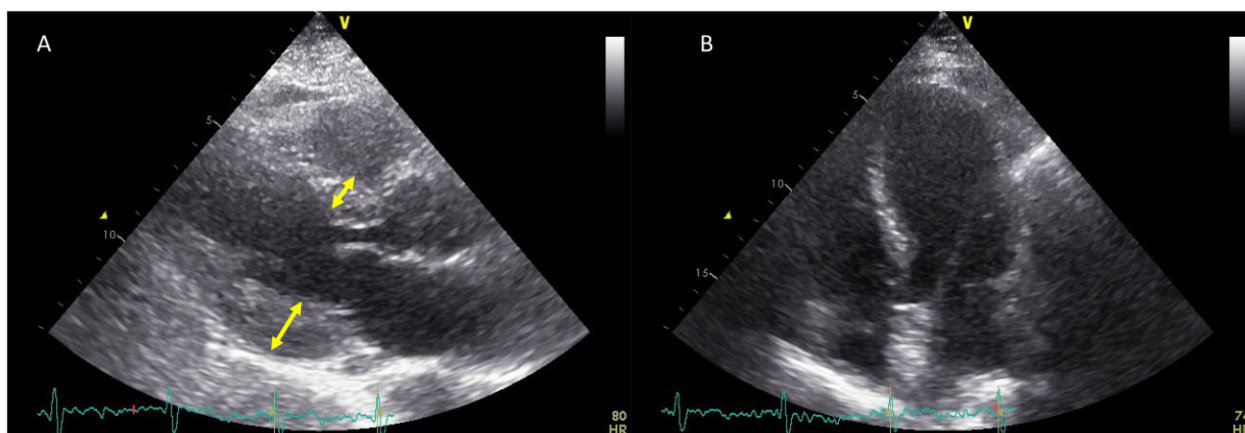
## Case 2

A 63-year old woman, sister of the first patient, was referred to the cardiology department of our hospital in August 2017. Relevant medical history included arterial hypertension, hypercholesterolaemia, transient ischaemic attack, and cerebrovascular accident secondary to paroxysmal atrial fibrillation (AF). She had been diagnosed with a non-ischaemic cardiomyopathy with reduced ejection fraction [left ventricular ejection fraction (LVEF) 25–30% (normal range 54–74%)] in May 2016. Complete work-up had been performed already. Coronary angiography had shown only very mild signs of coronary atherosclerosis and cardiac magnetic resonance imaging (MRI) suggested reduced LVEF secondary to a viral myopericarditis. Heart failure treatment was started with progressive improvement of cardiac function, leading to an estimated LVEF of 55% (normal range 54–74%) in October 2016. The patient did not mention that she had a sibling with cardiac amyloidosis.

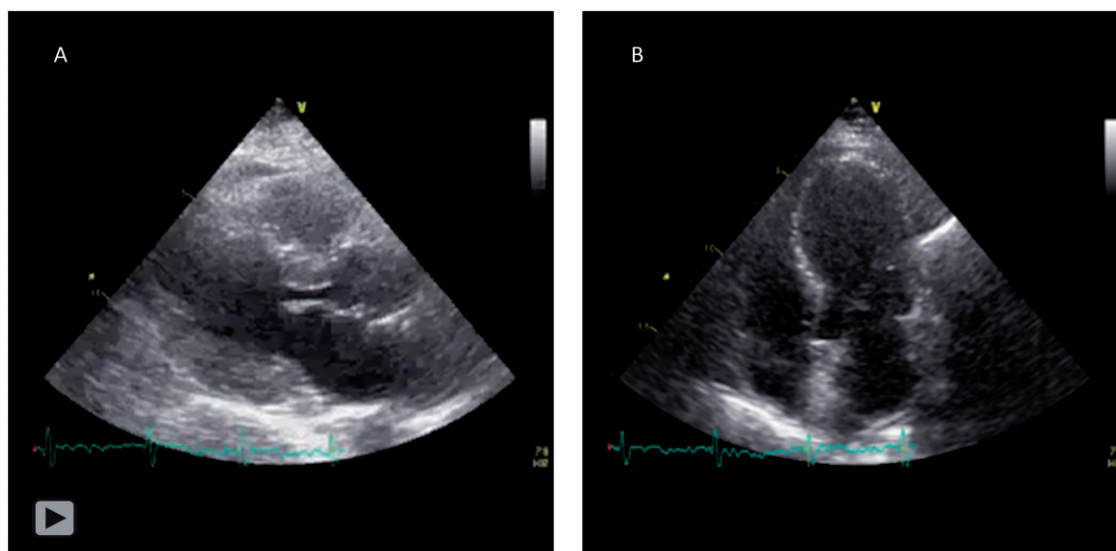
However, there remained a striking discrepancy between imaging findings and clinical evolution. Despite significant improvement of cardiac function (LVEF 55%), the patient continued to complain of shortness of breath, fatigue, exercise intolerance (New York Heart Association classification Grade II–III), and weight loss (25 kg over the course of a year). In August 2017, she was referred to the out-patient



**Figure 1** Electrocardiogram of Patient 1 showing sinus rhythm with incomplete right bundle branch block and relatively low voltages in peripheral leads.



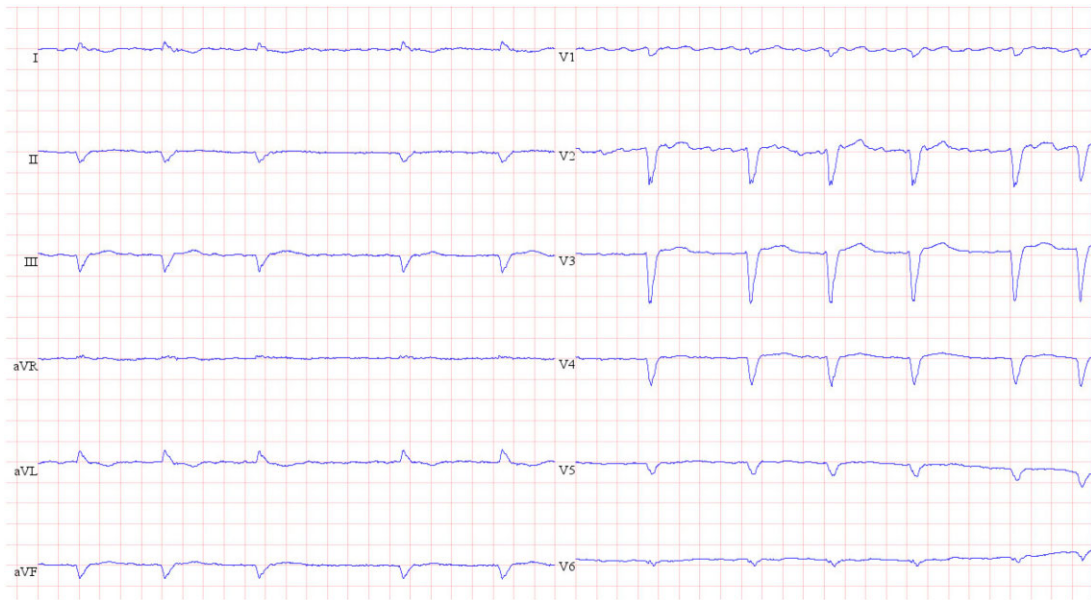
**Figure 2** Parasternal long-axis (A) and apical four-chamber view (B) on echocardiography of Patient 1 demonstrating left ventricular hypertrophy (thickness interventricular septum 13.5 mm, left ventricular posterior wall 12.2 mm (yellow arrows)). Left ventricular ejection fraction was judged at 60%.



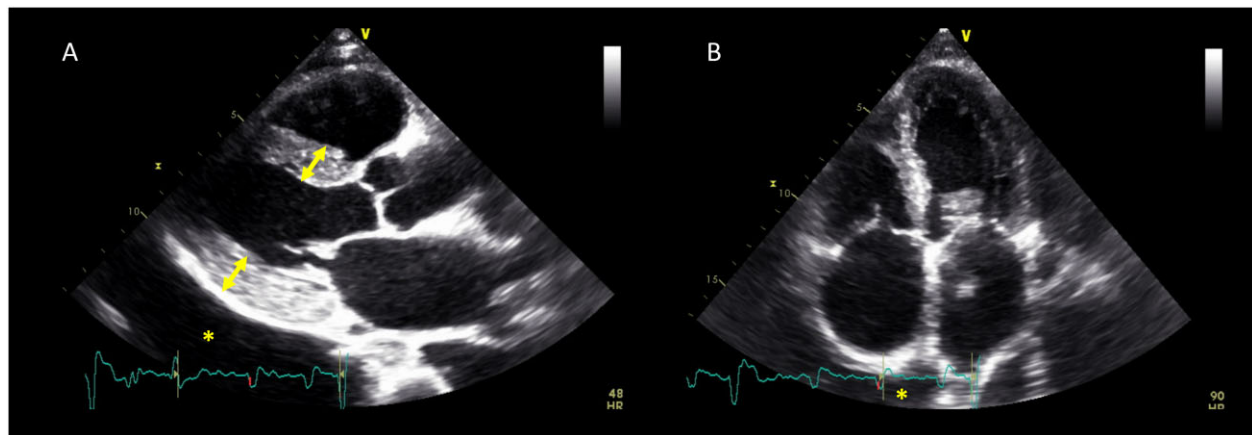
**Video 1** Parasternal long-axis (A) and apical four-chamber view (B) on echocardiography of Patient 1.

clinic of our cardiology department where she was found to have clinical signs of overt heart failure including bilateral pleural effusion and peripheral oedema. Her treatment at the time included spironolactone, angiotensin-converting enzyme-inhibitor, ivabradine, loop diuretics, amiodarone, apixaban, and atorvastatin. Treatment with beta-blocker had recently been suspended due to syncope and changed into amiodarone to better control her paroxysmal AF following rhythm control strategy and to exclude AF as contributing factor for her heart failure. Laboratory results revealed very high levels of NTproBNP (11 000 ng/L, normal value < 125 ng/L), raised troponin levels (hs-cTnT 0.170 µg/L, normally < 0.014 µg/L), and abnormal

liver tests [total bilirubin 1.49 mg/dL (normal value < 1.18 mg/dL); gamma-glutamyl transferase 187 U/L (normally < 40 U/L); alkaline phosphatase 120 U/L (normal range 35–105 U/L); aspartate transaminase 42 U/L (normally < 31 U/L), and alanine aminotransferase 31 U/L (normally < 31 U/L)]. On abdominal ultrasound, there were mild ascites. Electrocardiogram showed AF with a slow ventricular rate (65 b.p.m.) and low voltages (Figure 3). On echocardiography, she had LV hypertrophy with severely reduced LV systolic function (LVEF ±20%, normally 54–74%), high filling pressures, apical sparing on deformation imaging, and severe bilateral atrial dilatation (Figures 4 and 5; Video 2).



**Figure 3** Electrocardiogram of Patient 2 showing atrial fibrillation with slow ventricular response rate, broad QRS complexes and intra-ventricular conduction abnormalities.

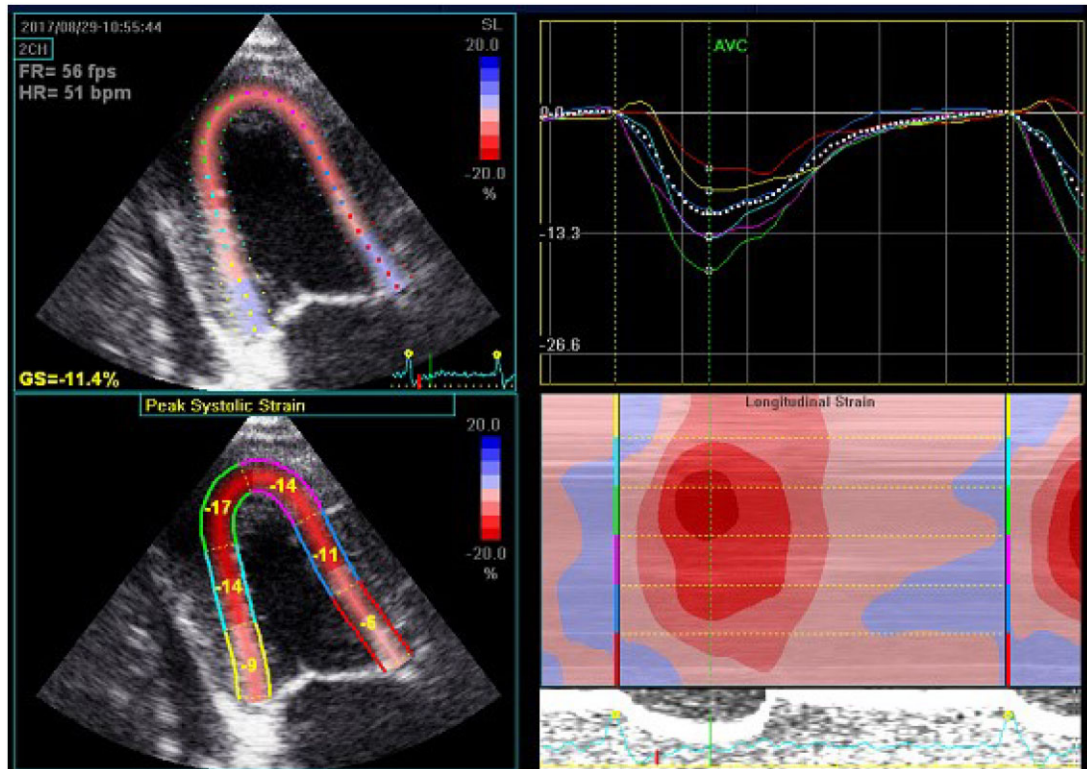


**Figure 4** Parasternal long-axis (A) and apical four-chamber view (B) on echocardiography of Patient 2 demonstrating left ventricular hypertrophy [thickness interventricular septum 13 mm, left ventricular posterior wall 16 mm (yellow arrows), pericardial effusion (\*), and severe bilateral atrial dilatation]. Left ventricular was calculated at 25% using biplane Simpson's method.

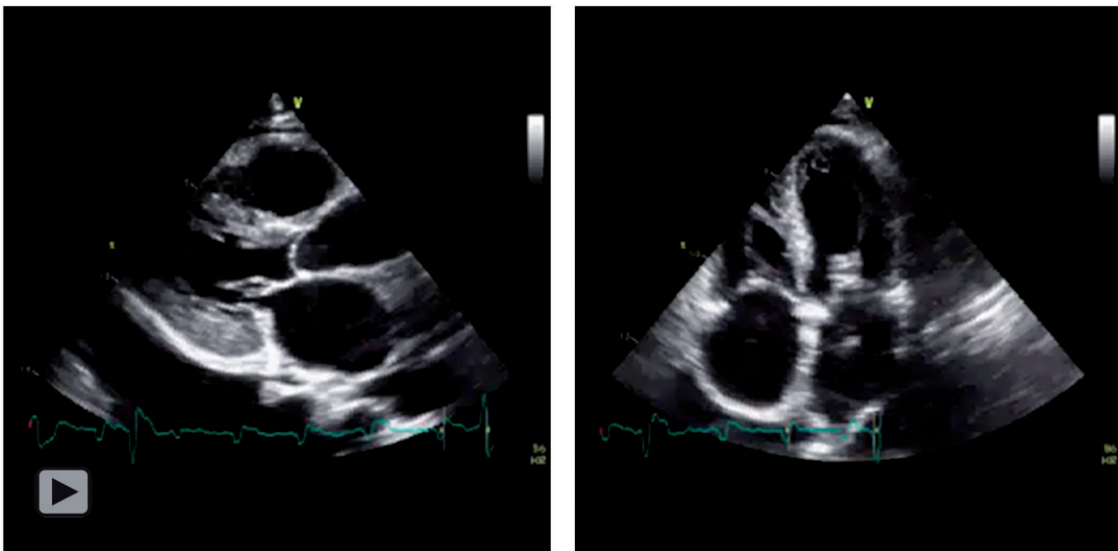
Based on these typical echocardiographic features, cardiac amyloidosis was suspected. Further blood and urine analyses revealed a monoclonal population of lambda light chains in the blood [serum free light chains (FLC) 149 mg/L; normal range 5.7–26.3 mg/L]. Cardiac MRI showed significant sub-endocardial late gadolinium enhancement and elevated T1 values on T1-colour mapping with severe biventricular systolic dysfunction (Figures 6 and 7; Video 3A–D), highly suggestive of cardiac amyloidosis.

Additional exploration with cardiac catheterization revealed raised intra-cardiac pressures on the left and right side of the heart (pulmonary capillary wedge pressure of 22 mmHg, normal value < 15 mmHg), and biopsies were taken. These stained positive on Congo red. Additional immunohistochemistry staining showed a predominance of lambda light chains in the amyloid deposits. Investigation of bone marrow showed a small monoclonal population of plasma cells (5%, normally < 2.7%) with a predominance of lambda

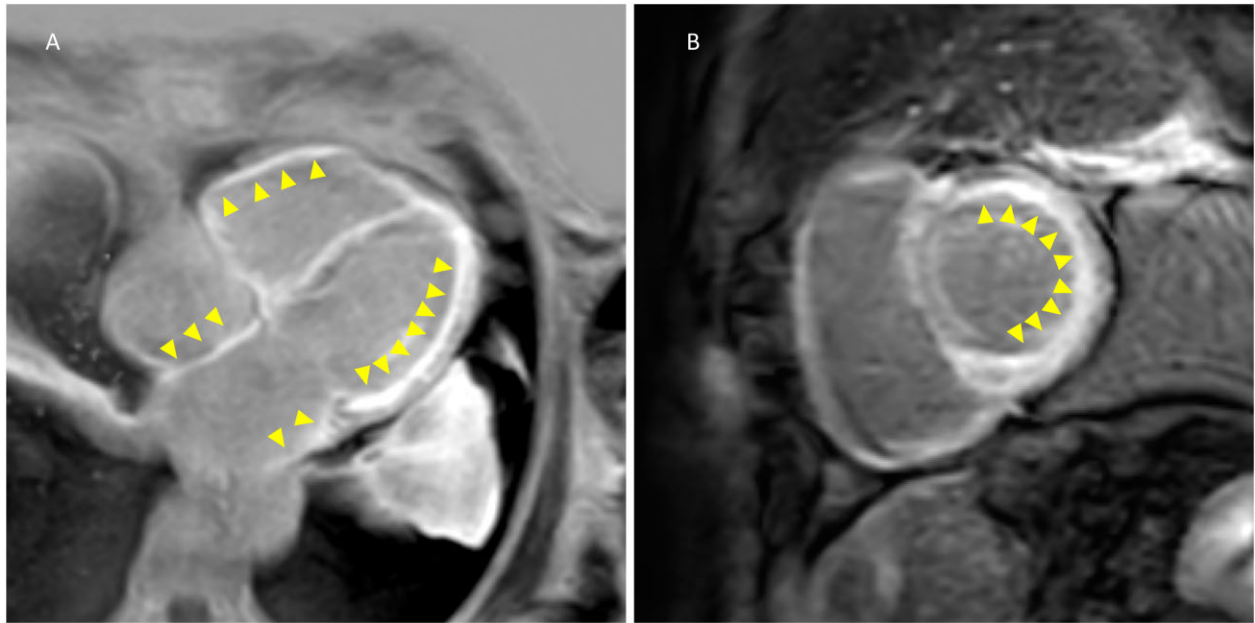




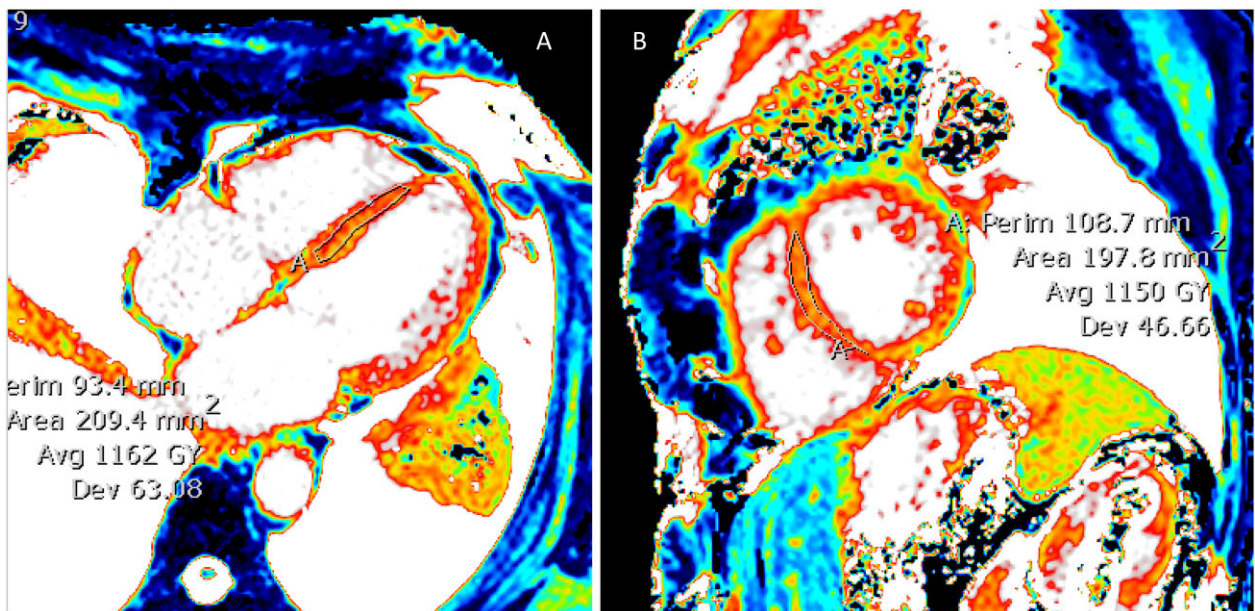
**Figure 5** Strain imaging of Patient 2 showing a severely reduced longitudinal function with apical sparing.



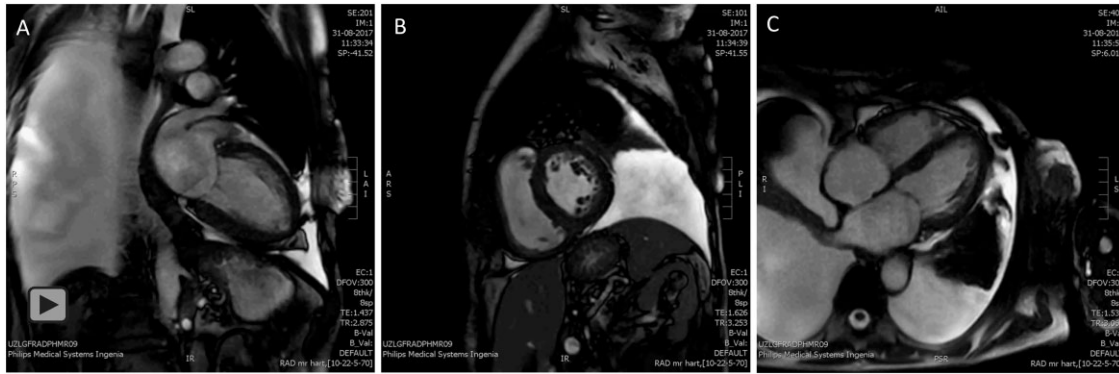
**Video 2** Parasternal long-axis (A) and apical four-chamber view (B) on echocardiography of Patient 2.



**Figure 6** Cardiac magnetic resonance imaging of Patient 2 Highly suggestive of cardiac amyloidosis with significant sub-endocardial late gadolinium enhancement in left ventricular, right ventricle, and both atria (yellow arrows), with some regions displaying transmural late gadolinium enhancement, a known factor portending worse prognosis. (A) Four-chamber view; (B) short-axis view.



**Figure 7** Cardiac magnetic resonance imaging of Patient 2 highly suggestive of cardiac amyloidosis on T1 colour mapping images (A and B; 1.5 T, modified look-locker inversion recovery sequence; normal native T1 values 965–1042 ms). Amyloid infiltration can be seen by elevated T1 values.



**Video 3** Cardiac magnetic resonance imaging of Patient 2 highly suggestive of cardiac amyloidosis showing biventricular systolic dysfunction (left ventricular ejection fraction 39%, right ventricular ejection fraction 35%) on Balanced Turbo Field Echo (BTFE): BTFE vertical long-axis view (A), BTFE short-axis view (B), BTFE horizontal long-axis view (C), and BTFE-MD2 (D).



**Video 3** (Continued).

light chains.  $^{99m}\text{Tc}$ -MDP scintigraphy only showed a very light staining in the myocardium.

Diagnosis of AL amyloidosis with severe cardiac involvement (Mayo Stage IIIb) was made.

A multidisciplinary team of cardiologists, heart transplantation specialists, transplantation surgeons, and haematologists decided that, given the poor prognosis, combined transplantation (stem cells–heart) was not a valid option. There was, however, an active wish for treatment from the patient and her family. Despite only very slim chances of success, treatment was started with melphalan–bortezomib–dexamethasone after initial treatment with intravenous diuretics and optimization of heart failure medication.

A few weeks later, the patient presented with acute dyspnoea, weight gain, and increased peripheral oedema due to progressive heart failure. The patient was hospitalized for the administration of intravenous diuretics. During hospitalization, there was a witnessed cardiac arrest. Immediate resuscitation was started but ultimately unsuccessful. The first rhythm detected during advanced life support cardiopulmonary resuscitation was pulseless electrical activity. The cause of death was most likely a malignant arrhythmia in a patient with severe cardiac dysfunction.

## Discussion

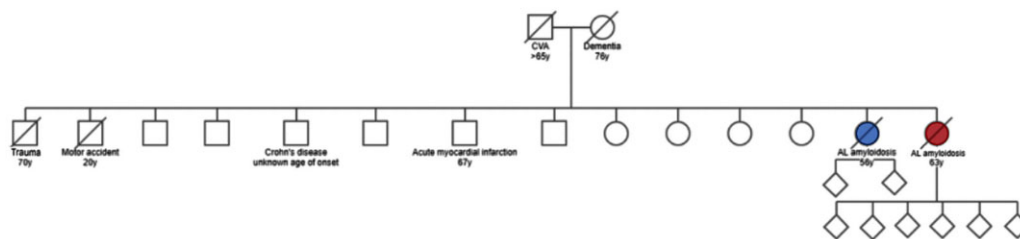
A systemic amyloidosis is a group of diseases caused by the deposition of insoluble protein aggregates in different organ tissues, eventually leading to organ dysfunction.<sup>1</sup> Virtually any organ can be affected, including the heart, the kidneys, liver, gastro-intestinal tract, autonomous, or peripheral nervous system.<sup>2</sup> The clinical presentation is diverse and varies according to which organs are affected and the extent of damage to these organs.

Cardiac amyloidosis refers to cardiac involvement with infiltration of amyloid fibrils in the myocardium, eventually leading to cardiac dysfunction and/or arrhythmias.<sup>2</sup> There are different types of amyloid fibrils that can infiltrate the heart. The two most common types affecting the heart are light-chain amyloidosis (AL amyloidosis) and transthyretin (TTR) amyloidosis [mutant (TTRm) or wildtype (TTRwt)].<sup>6</sup>

AL amyloidosis is caused by a, usually small, the population of clonal plasma cells that produce a monoclonal immunoglobulin light-chain (kappa or lambda) which folds incorrectly and deposits in different organs.<sup>2</sup> It is the most frequent type of systemic amyloidosis with cardiac deposition as the most frequent type of organ damage and the degree of cardiac involvement being the greatest predictor of prognosis.<sup>6</sup>

Certain types of systemic amyloidosis are hereditary. All those which have been described until now are inherited in a dominant way





**Figure 8** Family pedigree. Patient 1 in blue and Patient 2 in red. For deceased family members, cause of death and age of death are depicted. If alive, medical history was added with age of onset.

and are caused by a mutation resulting in the production of mutant proteins.<sup>7</sup>

AL amyloidosis has always been described as a sporadic disease caused by plasma cell dyscrasia.<sup>6</sup> However, familial AL amyloidosis has been reported occasionally. Miliani *et al.* reported a case of three siblings with AL amyloidosis in 1996. All three siblings presented with polyneuropathy that was associated with sicca keratoconjunctivitis in two of them and with a nephrotic syndrome in the third.<sup>8</sup> Gertz *et al.*<sup>9</sup> reported AL amyloidosis in three different families.

Benson *et al.* described a family with an immunoglobulin kappa AL amyloidosis due to a Ser131Cys mutation in the constant region of the kappa light-chain gene. However, the authors made a clear distinction between classical AL amyloidosis and the amyloidosis type in their case report. The first is the result of a plasma cell dyscrasia producing a monoclonal population of light chains, due to a particular conformation in the variable region ( $V_L$ ) of the light-chain predisposing to amyloid fibril formation when produced in excess. In the family Benson describes, amyloidosis was the result of a specific mutation in the constant region ( $C_L$ ) of the light-chain gene, which in a heterozygous individual, would be present in 50% of all serum IgG kappa antibodies.<sup>7</sup> Two other cases have reported a similar mutation (Ser177Asn) in the constant region of the kappa light chain (Solomon *et al.*<sup>10</sup> and Wally *et al.*<sup>11</sup>)

In this report, we describe two sisters with AL amyloidosis with cardiac involvement. To our knowledge, this has only been reported once before in first-degree relatives. Enqvist *et al.*<sup>3</sup> described the case of a father and his son both suffering from cardiac AL amyloidosis. Biochemical analysis of the fibril protein of both individuals revealed an AL lambda amyloidosis. Protein sequence analysis of the amyloid fibrils, revealed a lambda 3a amino acid sequence, with six amino acid substitutions compared to germline sequence for the father. Similar analysis for the son revealed a lambda 2a amino acid sequence, with three substitutions compared with the germline sequence.

In contrast, in our case report, the first sibling was diagnosed with isotype kappa light-chain AL amyloidosis, while the second sibling developed a lambda light-chain AL amyloidosis. The two sisters came from a family of 13 children. Known medical information about all family members is shown in Figure 8. One brother suffered an acute myocardial infarction at the age of 65 and underwent coronary bypass surgery. No other family member was known to suffer from severe cardiac problems. Based on the information available to us, no common environmental exposures were identified that may have

increased the risk of developing cardiac AL amyloidosis. The diagnostic molecular analysis did not reveal any pathological TTR mutations, though we cannot exclude that other, unknown mutation(s) are the underlying cause of the disease in these cases.

Taken together, our case report and Enqvist *et al.*,<sup>3</sup> raise the question of a potentially hereditary predisposition for the development of cardiac AL amyloidosis, or are these purely coincidental findings?

Furthermore, this case raises very relevant questions for remaining family members. Is screening necessary? If yes, from what age and using which tests?

As is often the case with very rare diseases, many unsolved questions remain. The case was discussed in a multidisciplinary context. Based on expert opinion, the following strategy was suggested: yearly screening of serum protein electrophoresis and serum FLC in first-degree relatives from the age of 40 onwards.

## Lead author biography



Sarah Cappuyns graduated as MD at KU Leuven in 2017 and first spent two years in clinical training as a resident of Internal Medicine. Her interests quickly veered towards oncology and the influence of genetics on cancer diagnosis, prognosis and treatment. She is now a PhD candidate in Digestive Oncology at KU Leuven focusing on unravelling the intricacies

of the tumour micro-environment and its interactions with the immune system. Her research addresses remaining clinical questions, ultimately paving the way towards improved, and more personalized patient care.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

## Acknowledgements

We would like to thank Prof. Evelyne Lerut for her advice on this case and sharing of her long-standing expertise as a pathologist.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** Patient 2 reported in this case is deceased. Despite the best efforts of the authors, they have been unable to contact the patient's next-of-kin to obtain consent for publication. Every effort has been made to anonymize the case. The authors confirm that witnessed verbal consent for submission and publication of this case report including images and associated text has been obtained from Patient 1 detailed in this case report. This has been discussed with the editors.

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**Conflict of interest:** None declared.

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