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GRAND ROUND
Heart failure

‘Here comes the story of the Hurricane’: a case report of AL cardiac amyloidosis and myocardial bridging

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Background Cardiac amyloidosis (CA) is a rapidly progressive infiltrative cardiomyopathy, whose role is emerging as a not-so-rare disorder leading to heart failure (HF). Myocardial bridge (MB) is the most common inborn coronary artery variant, and its clinical relevance is still matter of debate. The exceptional coexistence of these two conditions could accelerate disease progression and worsen the already compromised clinical conditions.

Case summary We present the case of a 76-year-old female patient experiencing relapsing HF decompensation and presenting to our centre with dyspnoea at rest and severe peripheral congestion. Echocardiogram showed severe concentric hypertrophy, severe biventricular contractile dysfunction, and third-degree diastolic dysfunction. Coronary angiography excluded epicardial atherosclerotic disease, though displaying a long intramyocardial course of left anterior descending artery. Physiological invasive test was achieved in terms of instantaneous wave-free ratio (iFR), both at baseline and after inotropic and chronotropic stimuli, and attested haemodynamic significance. Concurrently, the diagnostic flow chart for CA was accomplished, by means of both invasive (periumbilical fat biopsy, bone marrow aspiration) and non-invasive tests (^{99m}Tc-diphosphonate scintigraphy, serum-urine immunofixation) that confirmed the suspect of primary amyloidosis. Acute HF therapy was personalized according to the singularity of the case, avoiding both nitrates and beta-blockers, then first cycle of chemotherapy was started.

Discussion Our clinical case shows a unique interaction between infiltrative cardiomyopathy and coronary artery abnormality. Amyloidosis can contribute to the ischaemic burden of the MB and this may, in turn, abbreviate the path to HF decompensation.

Keywords Case report • Heart failure • Cardiac amyloidosis • Myocardial bridge • Functional intracoronary assessment

ESC Curriculum 2.3 Cardiac magnetic resonance • 6.2 Heart failure with reduced ejection fraction • 6.4 Acute heart failure • 6.5 Cardiomyopathy

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Learning points

- Cardiac amyloidosis is to be suspected in patients with otherwise unexplained severe cardiac hypertrophy and signs and symptoms of HF progression. Early diagnosis (and treatment) is mandatory to improve prognosis.
- Myocardial bridge is often an asymptomatic condition, but it can also be responsible for myocardial ischaemia and have a relevant clinical impact.
- Invasive functional assessment with iFR may probe the haemodynamic relevance of MB. Lowering of iFR after inotropic and chronotropic stimulation (shorter diastolic filling time) supports how the MB was responsible for inducible ischaemia.
- The AL type CA can be present even if serum protein electrophoresis is normal. The dosage of sFLC, serum-urine immunofixation, bone marrow aspiration, and periumbilical fat biopsy may help the diagnosis in case of high suspicion.
- The association of CA and MB is uncommon, and can lead to a worsening of clinical conditions due to their additive deleterious effects.

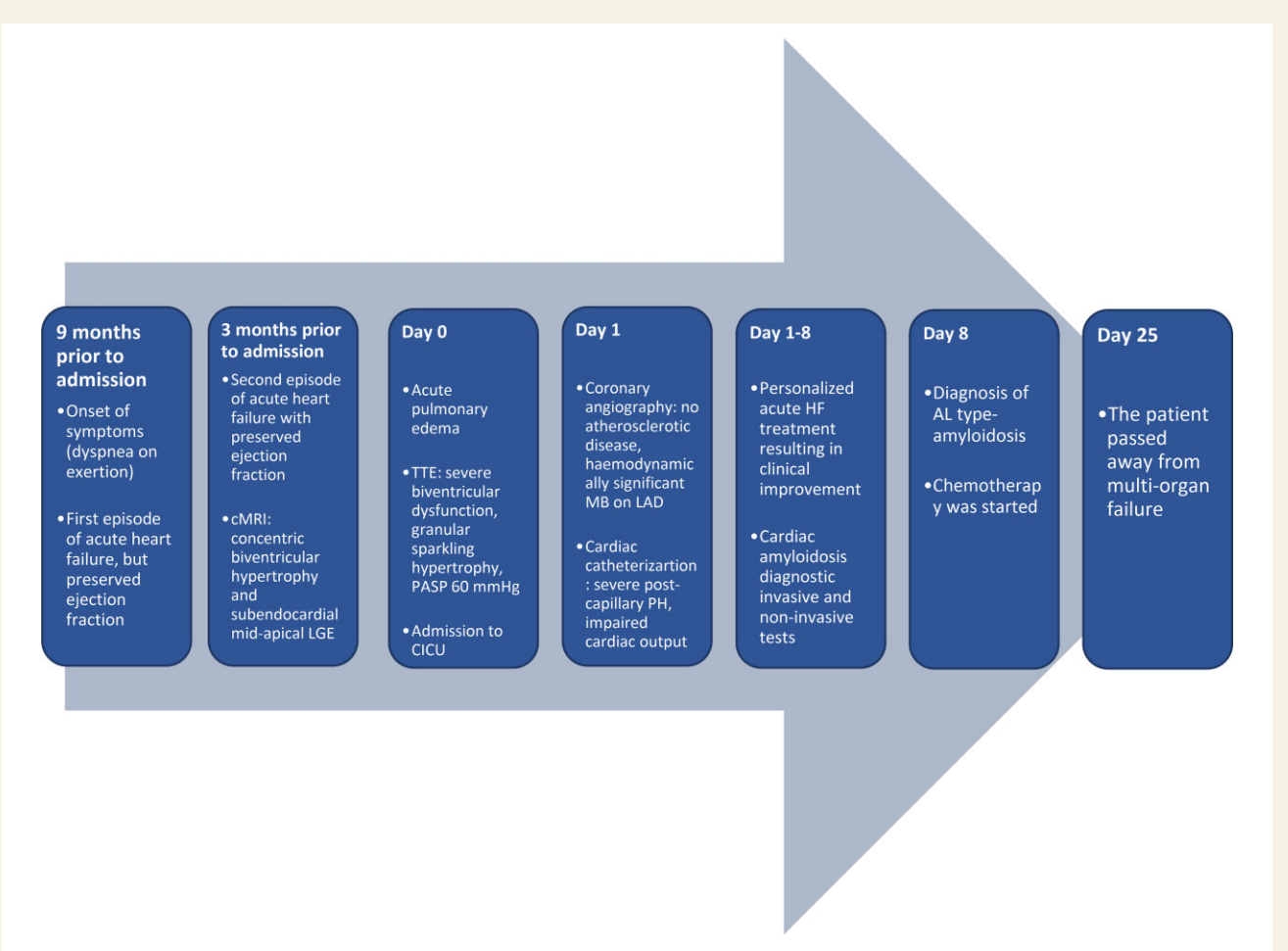
Primary specialities involved other than cardiology

Haematologist, radiologist, intensive care unit.

Introduction

Light chain (AL) amyloidosis is a haematologic disorder caused by the proliferation of an abnormal clone of plasma cells overproducing lambda or, less commonly, kappa light chains, freely secreted in the serum (sFLC).[1] The sFLC accumulates in different tissues (mostly soft tissues, kidney, and heart) and deposits as amyloid, leading to organ dysfunction. The AL amyloidosis is closely related to multiple myeloma, but these two conditions can also present separately.[2] Cardiac amyloidosis (CA) is a form of progressive infiltrative cardiomyopathy caused by amyloid deposition in the heart at different levels (i.e. myocardium and vessels) and this causes a progressive increase in wall thickness and stiffness and it can lead, in the most advanced phases, to heart failure (HF).[3]

Timeline



Myocardial bridging (MB) is a congenital variant in which a segment of an epicardial coronary artery, most frequently the left anterior descending (LAD) artery, takes a tunnelled course under a bridge of myocardium. Although MB is usually an asymptomatic bystander, growing evidence reports its heterogeneous clinical relevance, mainly associated with angina or other signs and symptoms of myocardial ischaemia.[4,5]

The MB is a quite common coronary artery variant (mean autoptic prevalence reported of 25%),[4] but its concomitant association with CA is a rare condition and, in case of severe myocardial pseudohypertrophy with tissue and vascular infiltration by amyloid fibrils,[6] these two separate entities could both cause myocardial ischaemia and worsen patients clinical conditions.

Case presentation

We present the case of a 76-year-old white woman admitted to the hospital for worsening dyspnoea and peripheral congestion. The medical history was relevant for arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, and recent SARS-CoV-2 pneumonia. Her home medications included furosemide (25 mg t.i.d.), amlodipine (5 mg o.d.), canrenone (50 mg o.d.), olmesartan (20 mg o.d.), and atorvastatin (20 mg o.d.).

The onset of symptoms insidiously arose over the previous 9 months, with two episodes of acute HF with preserved ejection fraction (EF), requiring hospitalization in other centres. The respective echocardiograms documented, indeed, only left ventricular (LV) hypertrophy, with normal global and regional LV contractility. After the second episode, which occurred 3 months before the admission to our hospital, a cardiac magnetic resonance imaging (cMRI) revealed a hypertrophic phenocopy with biventricular involvement and circumferential subendocardial late gadolinium enhancement, mainly in the mid-apical segments (*Figures 1 and 2*).

At admission, the patient was severely symptomatic for dyspnoea at rest (NYHA Class IV) and presented signs of right ventricular (RV) failure (lower limbs oedema and jugular vein distention). Fine bilateral basal crepitations were also present. Her vitals were as follows: heart rate 110 b.p.m., blood pressure 135/75 mmHg, SpO_2 94% in ambient air, and she was apyretic. The electrocardiogram showed sinus rhythm, first-degree atrioventricular block, Q waves, and low-voltage QRS complexes without R-wave progression (pseudo-infarction pattern) in pre-cordial leads (*Figure 3*). Blood tests revealed elevated NT-proBNP (10 794 pg/mL; n.v. $<$ 150 pg/mL) and moderately elevated high-sensitivity cardiac troponin I (236 ng/L, n.v. $<$ 37 ng/L).

A transthoracic echocardiogram was then repeated (*Figure 4*) and it revealed a severe LV hypertrophy (interventricular septum [IVS] thickness 18.5 mm, relative wall thickness 0.94, left ventricular mass index 176 g/m^2) with 'granular sparkling' aspect, severe left ventricular contractile dysfunction (EF 34%; left ventricular outflow tract velocity time integral 9 cm; stroke volume index 16.5 mL/m^2), third-degree diastolic dysfunction with elevated LV filling pressures (*E*/*A* 2.57, *E*/e′ 32.4; *Figure 5A and B*), dilated RV with severe contractile dysfunction (TAPSE 12 mm, RV-FAC 14%) and significant pulmonary arterial hypertension (estimated systolic pulmonary arterial pressure of 60 mmHg). Coronary angiography revealed an MB with a long and severe systolic narrowing ('milking') of the proximal/mid-LAD epicardial artery without any evidence of coronary artery disease (*Figure 6A–D* and Supplementary material) Invasive functional assessment with instantaneous wave-free ratio (iFR) was performed to probe the haemodynamic impact of MB:iFR was 0.88 at baseline (n.v. $>$ 0.89), lowering to 0.82 after inotropic and chronotropic stimulation by intravenous dobutamine and atropine. These results were suggestive for an MB responsible for inducible ischaemia. Moreover, heart catheterization documented severe pulmonary

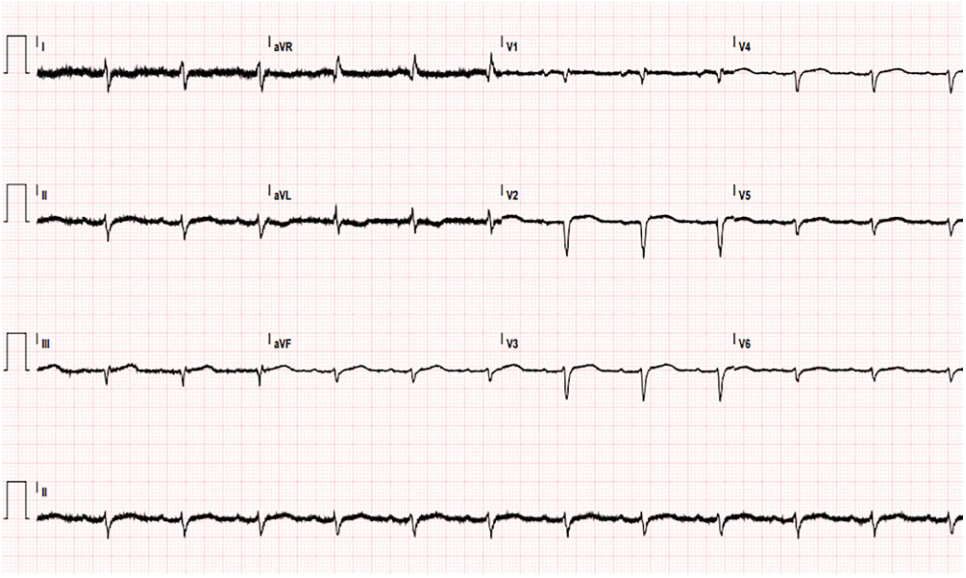


Figure 1 The electrocardiogram shows sinus rhythm, first-degree atrioventricular block, Q waves, and no R-wave progression (pseudo-infarction pattern) in pre-cordial leads.

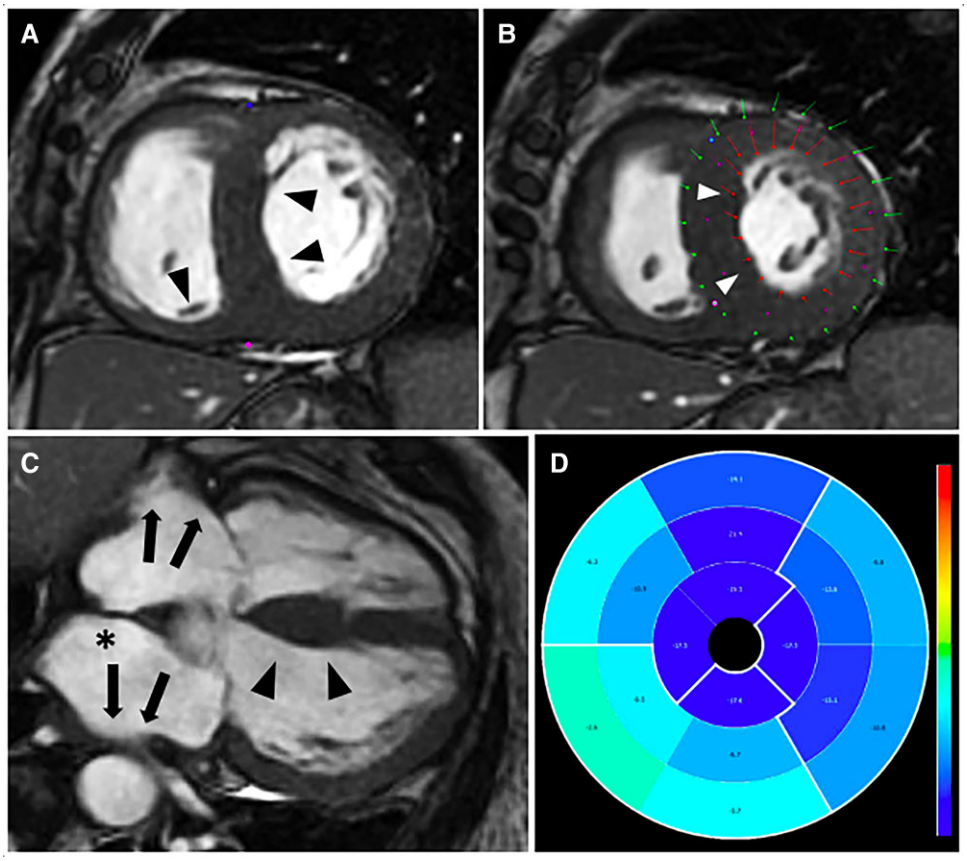


Figure 2 (*A* and *C*) Steady-state free precession cine images acquired in diastolic phase show an asymmetric hypertrophic phenotype (short axis and horizontal long axis, respectively). Black arrowheads highlight a prevalent hypertrophy of mid-basal septal segments and basal inferior wall of right ventricle. Inter-atrial septum (black asterisk) and biatrial wall (black arrows) shows regular thickness. (*B*) Boundary points representation of cardiac magnetic resonance tissue tracking analysis (Circle, cvi42, Calgary, Canada; version 5.11.4): epicardial and subendocardial deformability, respectively, represented by external and internal lines and dots. Short-axis systolic acquisition: septal segments clearly show the lower deformability (white arrowheads). (*D*) Colour map representation of cardiac magnetic resonance tissue tracking analysis: darker blue colours represent a higher myocardial deformation; lighter blue and yellow-to-red colours represent a lower deformation. Apical segments show regular deformability ('apical-sparing pattern'). Overall systolic function was moderately depressed.

arterial hypertension, mainly post-capillary (pulmonary capillary wedge pressure 37 mmHg, mean Pulmonary arterial pressure 46 mmHg, pulmonary vascular resistance 3.56 WU), elevated LV end-diastolic pressure (40 mmHg), cardiac output 2.54 L/min, cardiac index 1.7 L/min/m^2, cardiac power output 0.45 W, pulmonary artery pulsatility index 1.9.

The patient also underwent non-invasive and invasive tests in order to confirm the diagnosis of CA, suspected on the basis of transthoracic echocardiography and cMRI: ^{99m}Tc-diphosphonate scintigraphy revealed no myocardial uptake of the isotope, ruling out cardiac ATTR (transthyretin) amyloidosis; of note, the serum protein electrophoresis showed no apparent qualitative alterations, but it detected lambda-type (λ) monoclonal immunoglobulin-free light chains (FLC; lambda 643.5 mg/L, n.v. = 5.7–26.3 mg/L; ratio kappa/lambda 0.02, n.v. = 0.26–1.65), which was confirmed by the serum-urine immunofixation. Bone marrow aspiration showed high percentage of plasma cells (5%) and, finally, periumbilical fat biopsy confirmed the diagnosis of CA type AL, due to multiple myeloma.

During the hospitalization the patient suffered from acute worsening of HF with acute pulmonary oedema (NT-proBNP increased to 15 500 pg/mL), requiring intravenous diuretics and non-invasive ventilation cycles (administered in cardiac intensive care unit). Nitrates were avoided due to the concomitant presence of MB. Low-dose beta-blockers were initially considered as conservative strategy to treat MB to increase diastolic filling time, but this option was early discarded. In case of CA with severe diastolic dysfunction, slowing heart rate could in fact be counterproductive because, due to an alteration of compliance and reduction in stroke volume, the cardiac output can be maintained within normal ranges only by an increase of heart rate. The patient also developed an acute renal failure requiring continuous haemodiafiltration (creatinine levels increased from 0.6 to 2.11 mg/dL, n.v. = 0.67–1.17 mg/dL, and anuria occurred). The case was collectively discussed in heart team, also with haematologists: implantable cardioverter defibrillator therapy was not recommended because of NYHA Class IV refractory to pharmacological therapy; considering the age >70, LVEF < 40%,

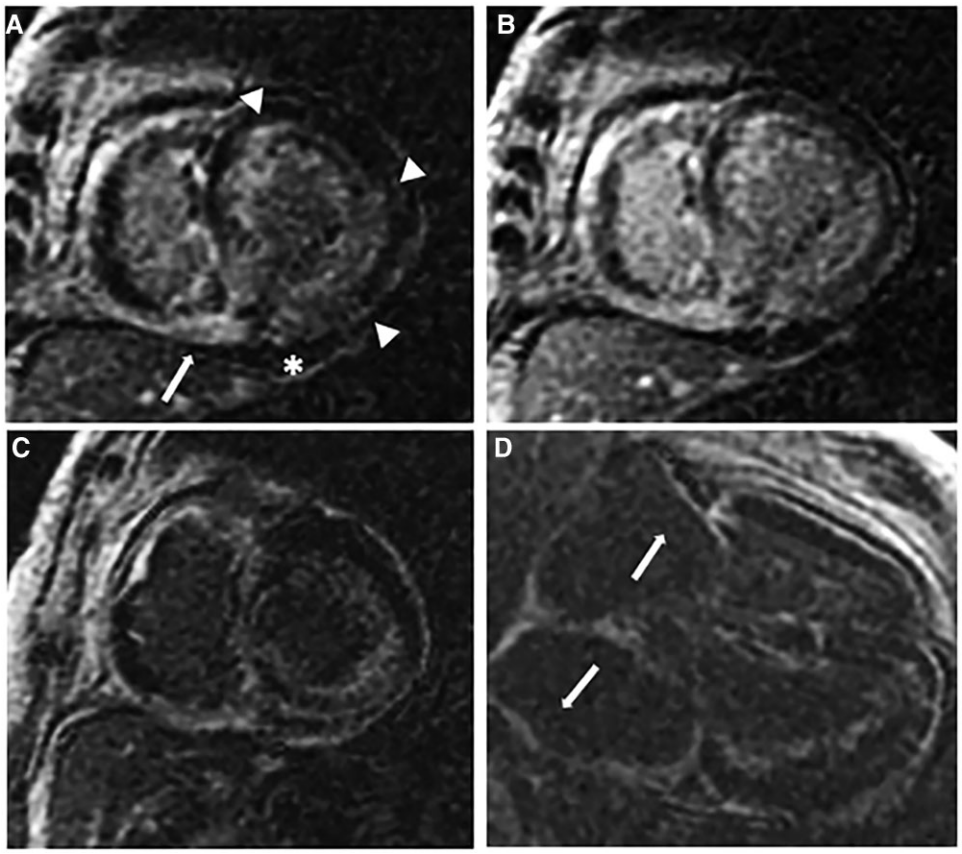


Figure 3 Two-dimensional myocardial delayed enhancement sequences acquired in systolic phase in both short-axis (*A–C*) and horizontal long-axis planes (*D*). (*AC*) The same short-axis 2D myocardial delayed enhancement slice acquired with different inversion time. Diffuse subendocardial enhancement (white arrowhead) is highlighted in basal segments with transmural involvement in mid-basal inferior segments (white asterisk). Marked enhancement is highlighted also in right ventricle and atrial wall (white arrows). Diffuse subendocardial late gadolinium enhancement pattern is typically present in patients with cardiac amyloidosis.

Eastern Cooperative Oncology Group performance score > 2 and NYHA class > 2, the patient was also considered not eligible for an autologous stem-cell transplantation. Combination chemotherapy of bortezomib and cyclophosphamide was instead started.

Despite intensive care and chemotherapy, the patient's clinical conditions progressively worsened and led to a multiorgan failure until, after 2 weeks of intensive care management, unfortunately she passed away.

Discussion

The AL-CA is an underestimated type of infiltrative cardiomyopathy, caused by the deposition of amyloid fibrils at the cardiac level, and it can progressively lead to HF.[7] In this case, the EF of the patient was 60% 9 months before the admission and then rapidly decreased to 34%. Improvements in diagnostic tools make the reduction of time to diagnosis possible, so that the treatment can start in the initial stages of the disease and improve the prognosis.[8] In the presented case, despite cMRI already documented signs of infiltrative cardiomyopathy, the patient was referred to our hospital only after 3 months. This delay in diagnosis and treatment could have therefore influenced the prognosis. The patient, indeed, presented to us with severe symptoms and signs of HF, as also confirmed by the haemodynamic parameters registered during heart catheterization, with significant pulmonary and peripheral congestion, such as to require non-invasive ventilation and intravenous diuretics in cardiac intensive care unit. These were all signs of an advanced, rapidly progressive form of CA. Interestingly, the serum protein electrophoresis was apparently normal, but an abnormal production of lambda FLCs was detected (both as absolute value and kappa/lambda ratio), corroborating the hypothesis of AL-CA, then confirmed by the periumbilical fat biopsy. In addition, advanced phases of CA are well known to cause severe microangiopathy causing a constant impairment of tissue perfusion. This can lead to diffuse myocardial ischaemia or even acute coronary syndromes in the absence of classical epicardial disease. Microvascular impairment in CA can occur in several ways, since amyloid deposition can imply a direct vessel infiltration, an interstitial extrinsic compression, or even an endothelial dysfunction.[9,10] On this basis, the myocardial fibrosis and therefore the LGE pattern revealed by the cMRI could, at least in part, be also induced by microvascular infiltration and dysfunction.[11,12]

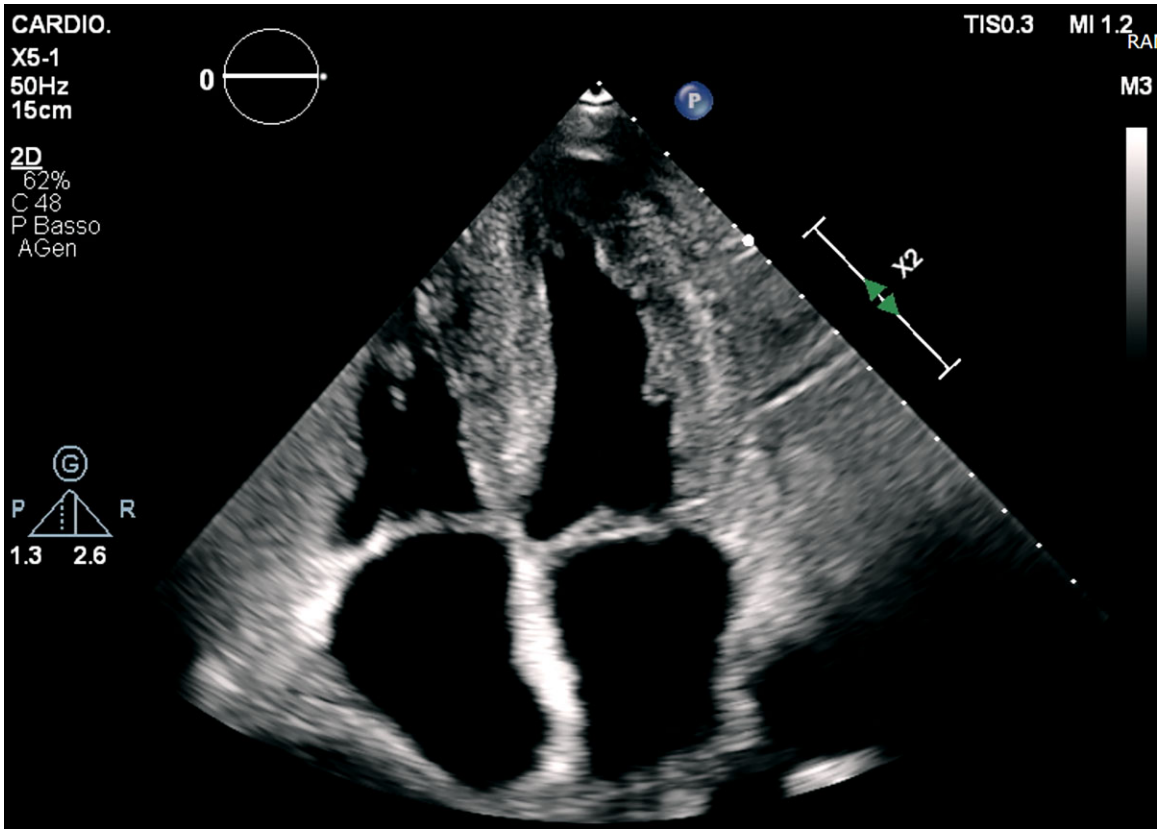


Figure 4 Transthoracic echocardiography showing severe concentric hypertrophy. Two-dimensional four-chamber apical view of the left ventricular showing severe hypertrophy, with an inter ventricular septum (IVS) of 18.5 mm.

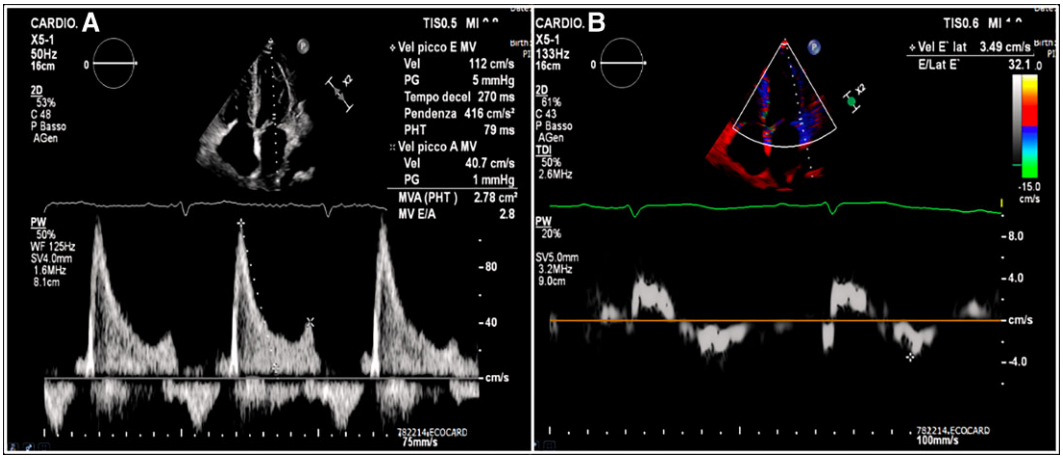


Figure 5 Transthoracic echocardiography evaluating diastolic function. (*A*) Pulsedwave Doppler with the sample volume at the left ventricular inflow (mitral valve leaflet tip) revealing a third-degree diastolic dysfunction (restrictive pattern). (*B*) Tissue Doppler imaging of the left ventricular confirming very high left ventricular filling pressure.

The MB is typically a benign and asymptomatic condition, but severe bridging may trigger myocardial ischaemia.[13] The wall shear stress caused by the long-standing compression relaxation of the tunnelled artery induces in fact epicardial and microvascular endothelial dysfunction,[14] associated with an increased expression of vascular cell adhesion molecules and reactive oxygen species production.

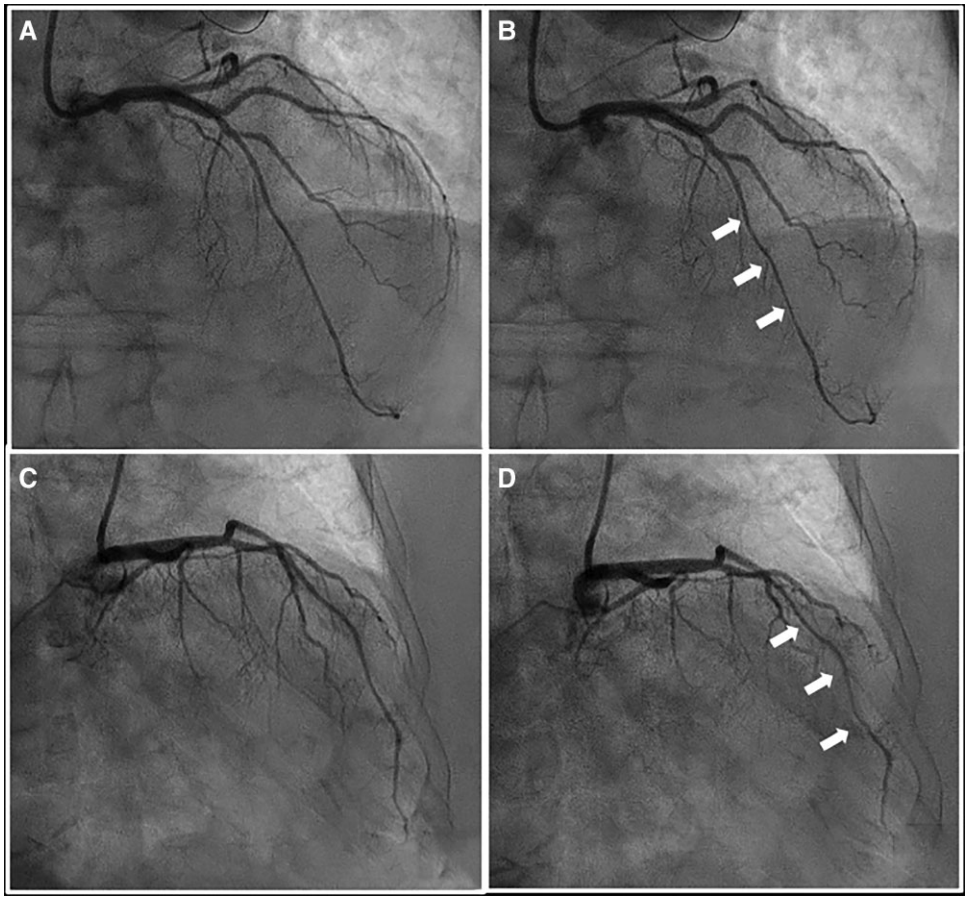


Figure 6 Coronary angiography revealing a long left anterior descending myocardial bridge. (*A*) Left cranial projection in diastole; (*B*) left cranial projection in systole; (*C*) right projection in diastole; (*D*) right projection in systole. White arrows indicate the tract of myocardial bridge with a long and severe systolic narrowing ('milking') of the proximal/mid-left anterior descending epicardial artery.

These events promote the development of a profibrotic and proinflammatory environment[15,16] that induces a chronic reduction of global myocardial perfusion.[17] In our case, MB was not associated with anginal symptoms, but it might have caused silent myocardial ischaemia as highlighted by the invasive functional assessment with iFR, which proved the haemodynamic significance of MB.[18] Moreover, the lowering of iFR after inotropic and chronotropic stimulation (shorter diastolic filling time) supports how MB was responsible for inducible ischaemia. Rates of MB are much higher in patients with hypertrophic cardiomyopathy than the general population.[4] In our case, the progression of LV pseudohypertrophy, supported by the progressive myocardial and vascular infiltration by amyloid fibrils, increased myocardial thickening, and, probably, epicardial coronary artery compression, thus improving the haemodynamic significance of MB.

Light chains in AL-CA are moreover cardiotoxic by themselves, as they induce oxidative stress and lysosomal dysfunction and disrupt autophagic flux causing cardiomyocyte death.[19] As discussed, the association of CA and MB probably exacerbated myocardial ischaemia and this, in addition to the underlying advanced HF already induced by CA, was a possible mechanism of further clinical conditions worsening.

This case therefore shows a singular association between AL type CA and MB, underlining how these two entities might worsen each other. The most common clinical manifestation of CA is progressive HF, but the amyloid deposition and the resulting cardiac pseudohypertrophy may also exalt the compression of a tunnelled artery, thus increasing myocardial ischaemia and, in case of advanced disease, promoting rapid clinical worsening.

Lead author biography

Doctor Cappannoli graduated in Medicine and Surgery in 2017 at Catholic University of the Sacred Heart (Rome) and he is currently taking his specialization in cardiology at the same institution. He is focusing his training on the field of heart failure, ischaemic heart disease, and invasive techniques and he is currently in training to become an interventional cardiologist. He is also attending the

postgraduate course on heart failure at the Royal Brompton Hospital, London. Actively involved in basic and translational research sciences as well as in clinical research, he has already authored more than 15 peer-reviewed manuscripts indexed in PubMed, Scopus, and Web of Sciences. He has also presented several original works, abstracts, and posters in cardiology congresses and international meetings.

Supplementary material

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

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Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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Data availability

The data underlying this article are available in the article and in its online Supplementary material.

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