

Unexplained heart failure with preserved ejection fraction diagnosed as amyloidosis of the heart

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<https://doi.org/10.26599/1671-5411.2026.05.008>

A 71-year-old man with a 30-year history of hypertension and a prior percutaneous coronary intervention (PCI) with two stents implanted in the left anterior descending artery 12 years ago for angina pectoris presented with a 6-month history of progressive palpitations and dyspnea. He had remained stable on regular medication and surveillance since the PCI. However, during this symptomatic period, repeat coronary angiography showed no significant stenosis, and his symptoms were refractory to optimized medical therapy. Multiple evaluations at other hospitals failed to establish a definitive diagnosis. One month prior to admission, outpatient echocardiography revealed a preserved ejection fraction (52%), biatrial enlargement, and left ventricular hypertrophy with a maximal interventricular septal thickness of 1.90 cm. Speckle-tracking echocardiography demonstrated reduced strain from the basal to mid left ventricular segments with apical sparing (global longitudinal strain: -10.7%). Notably, over the preceding six months, his blood pressure had spontaneously normalized, leading him to discontinue his anti-hypertensive medication. There was no family history of inherited disorders.

On admission, laboratory tests showed elevated myoglobin (140.0 ng/mL; normal 23–112 ng/mL) and NT-proBNP (2610.0 pg/mL; normal 300–900 pg/mL) (Figure 1A). Complete blood count revealed anemia with reduced erythrocytes ($3.24 \times 10^{12}/L$; normal $4.30\text{--}5.80 \times 10^{12}/L$) and hemoglobin (104 g/L; normal 130–175 g/L). Biochemistry indicated hypoalbuminemia (35.5 g/L; normal 40–55 g/L). Electrocardiography demonstrated left axis deviation, intraventricular conduction delay, ST-segment elevation (0.1–0.4 mV in V1–V4), and T-wave inversion in leads I and aVL (Figure 1B). Chest X-ray

showed bilateral lower-lung interstitial opacities and cardiomegaly. 24-h Holter monitoring detected intermittent first-degree AV block and sinus arrest (longest RR interval 2.578 s). Echocardiography revealed preserved ejection fraction (64%), persistent symmetric left ventricular wall thickening (Figure 1C), restrictive filling (Figure 1D), and impaired global longitudinal strain (-10.7%) with apical sparing (Figure 1E), unchanged from one month earlier. Cardiac magnetic resonance (CMR) confirmed biatrial enlargement, septal hypertrophy (Figure 1F), and diffuse subendocardial/intermuscular delayed enhancement (Figure 1G), along with a small pericardial effusion. Finally, 99mTc-PYP scintigraphy (SPECT) yielded a visual score of 3 with a heart-to-contralateral (H/CL) ratio of 1.5 (Figure 1H). Further laboratory evaluation revealed elevated serum IgA (33.00 g/L; normal 1.00–4.20) and immunoglobulin lambda light chains (10.8 g/L; normal 1.0–4.2 g/L) (Figure 1I), alongside a decreased complement C3 level (0.646 g/L; normal 0.700–1.400 g/L). Serum immunofixation and protein electrophoresis revealed an increased γ -globulin fraction (34.60%) and decreased α -2-globulin and albumin levels. Moreover, 24 h urine immunofixation electrophoresis was positive for λ light chain, IgA, and ELP, with M-protein deposition (14.2 g/L). Bone marrow cytology showed 15% plasma cells (Figure 1J), and immunophenotyping confirmed a monoclonal plasma cell population. Endomyocardial biopsy was performed after obtaining informed consent (Figure 1K). Histopathological analysis showed positive staining for both Congo red and oxidized Congo red. Immunohistochemistry results were as follows: Kappa (-), Lambda (+). The pathological diagnosis was confirmed as myocardial amyloidosis (AL-type).

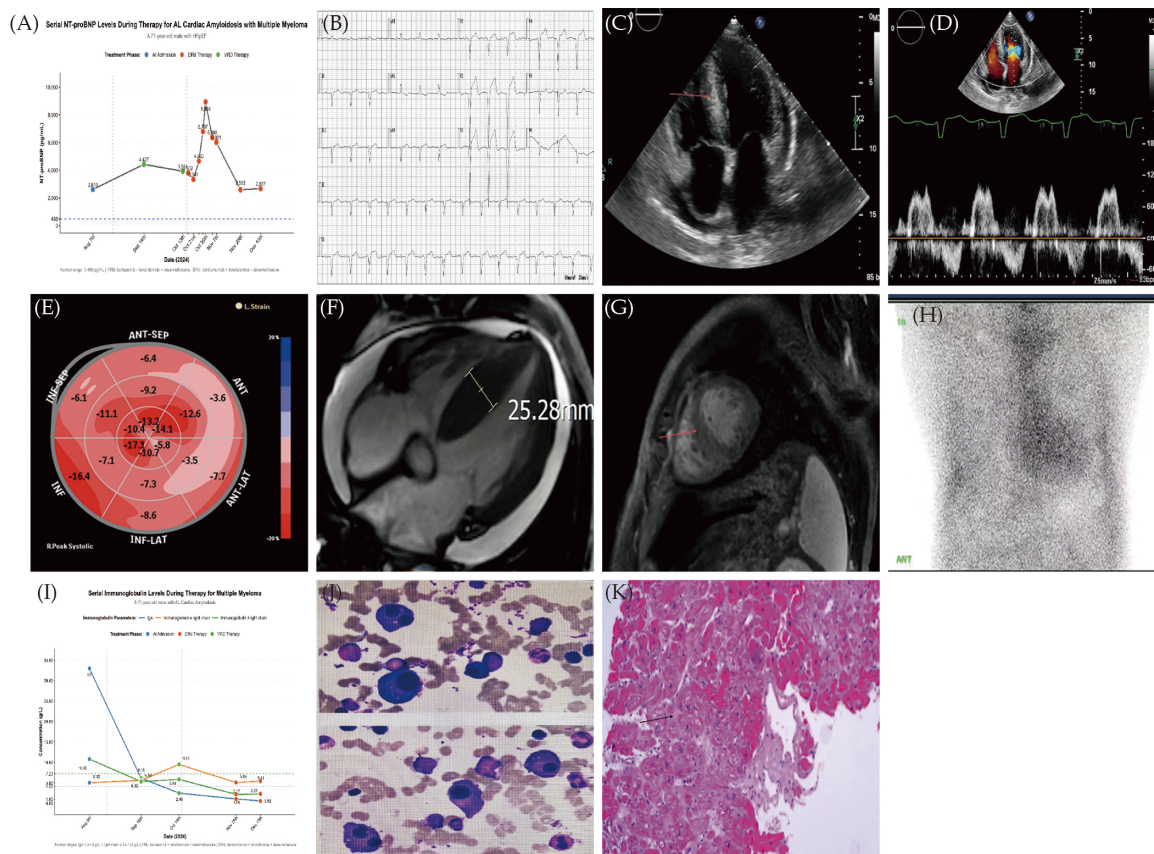


Figure 1 Diagnostic and follow-up findings in a patient with AL cardiac amyloidosis. (A): Serial NT-proBNP trends during treatment: largely stable, with a prominent elevation coinciding with pulmonary infection in the follow-up period. (B): The ECG showed Intraventricular block with ST-T segment changes in leads V1-V4 and T-wave inversion in leads I and AVL. (C): The four-chamber apical view shows dilation of the left and right atria, symmetric thickening of the walls of the left ventricle, and significant thickening of the interventricular septum (indicated by the red arrow). (D): Transthoracic echocardiography shows a restrictive left ventricular filling disorder with a mitral orifice E/A < 1 and a tricuspid orifice E/A < 1 measured by pulsed Doppler. (E): Speckle-tracking echocardiography demonstrates diminished strain indices in the basal and mid-segments of the left ventricular walls, with apical sparing, which is frequently denoted as the “cherry-on-top” appearance. (F): CMR demonstrated remarkable thickening of the interventricular septum, with the maximum measured thickness reaching 25.28 mm. (G): Delayed-phase cardiac magnetic resonance imaging revealed diffuse delayed enhancement in the left ventricular endocardium and between the myocardial walls (indicated by the red arrows). (H): ^{99m}Tc -PYP imaging for myocardial amyloidosis was negative. (I): Serial levels of IgA and immunoglobulin light chains (λ and κ) during treatment, demonstrating an overall downward trend consistent with hematologic response. (J): Bone marrow cytology findings were consistent with a myeloid picture characteristic of multiple myeloma. (K): Microscopic examination of the myocardial biopsy showed atrophic degeneration of myocardial fibers. Some cells presented with vesicular nuclear changes. There was interstitial fibrous hyperplasia, and homogeneous eosinophilic - stained material was visible (pointed out by the black arrows).

Following a comprehensive evaluation, the patient was ultimately diagnosed with multiple myeloma (IgA λ type, DS stage IIA, ISS stage II) accompanied by AL cardiac amyloidosis. After receiving one cycle of the bortezomib, lenalidomide, and dexamethasone (VRD) regimen, the patient was discharged. Guideline-directed medical therapy for heart failure was continued, including sacubitril/valsartan (25 mg twice daily), spironolactone (20 mg once daily), furosemide (20 mg once daily), and dapagliflozin (10 mg once daily). Subsequent follow-

up evaluations demonstrated a significant hematological response and stable cardiac function, indicating a favorable treatment outcome.

Amyloidosis is characterized by the misfolding and aggregation of specific precursor proteins into insoluble, protease-resistant amyloid fibrils. These fibrils deposit extracellularly in tissues, leading to progressive cellular damage and organ dysfunction. The disease can be categorized by distribution (focal or systemic) or by the type of precursor protein. To date, 36 distinct amyloidogenic



proteins have been identified, with immunoglobulin light chain (AL) and transthyretin (ATTR) being the most common.^[1] Cardiac amyloidosis (CA) refers to the deposition of amyloid fibrils formed by misfolded abnormal precursor proteins in the extracellular spaces of cardiomyocytes. Clinically, it primarily manifests as heart failure and various arrhythmias.^[2] AL-CA is characterized by excessively clonally expanded CD38⁺ plasma cells producing misfolded amyloid light chains. These form insoluble amyloid fiber oligomers that deposit in cardiac tissue, leading to structural and functional impairment of the heart. AL-CA predominantly affects males, with studies indicating the highest prevalence among patients aged ≥ 65 years, reaching 42.6%.^[3] Generally, AL-CA carries the poorest prognosis among cardiac amyloidoses, with the extent of cardiac involvement and disease staging playing critical roles.

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome driven chiefly by impaired left ventricular diastolic function. While often linked to comorbidities like hypertension, diabetes, and obesity, a subset of cases results from infiltrative cardiomyopathies such as CA. Clinical clues that should raise suspicion for CA in HFpEF include advanced age, elevated BMI, increased NT-proBNP and troponin, left ventricular hypertrophy, and unexplained normalization or reduction of blood pressure.^[4] This case highlights that a protracted diagnostic odyssey with HFpEF as the initial presentation underscores the diagnostic challenge of CA, for which echocardiography and CMR have become indispensable in achieving a timely diagnosis.

Typical features of CA include low-voltage QRS complexes on ECG, which are often discordant with echocardiographic left ventricular (LV) hypertrophy, and frequent conduction abnormalities. However, the absence of low QRS voltage does not exclude CA, necessitating a multimodal approach with echocardiography and cardiac magnetic resonance (CMR). Characteristic echocardiographic findings of CA include symmetrically thickened LV walls (> 1.2 cm) without other identifiable cause and impaired longitudinal strain with apical sparing – the “apical cherry” sign.^[5] Other frequently observed features comprise a normal or small LV cavity, granular myocardial hyperreflectivity, biatrial enlargement, restrictive diastolic filling, and often a small pericardial effusion. Tissue Doppler velocities of the mitral annulus (s', e', a' each < 5 cm/s) further support the diagnosis.^[6] On CMR, typ-

ical patterns consist of subendocardial or transmural late gadolinium enhancement (which may also involve the atria, valves, or right ventricle), non-obstructive hypertrophy, and markedly elevated native T1, T2, and extracellular volume (ECV).^[7] In our patient, an elderly male without personal/family history of amyloidosis or classic systemic manifestations, the ECG showed intraventricular conduction delay (though without low QRS voltage), and 24-h Holter monitoring revealed intermittent AV block and sinus pauses. Echocardiography demonstrated symmetric LV wall thickening, a granular myocardial texture, diastolic dysfunction, and apical-sparing strain. CMR confirmed septal hypertrophy with diffuse subendocardial/intramural late enhancement. Given this presentation of hypertrophy and HFpEF, differentiation from hypertrophic cardiomyopathy (HCM) and its phenocopies was essential.

HCM typically presents with asymmetric left ventricular hypertrophy, and more than half of patients exhibit HFpEF. Characteristic ECG findings include broad P waves, left axis deviation, increased QRS voltage, and ST-T abnormalities. Echocardiography often shows asymmetric LV hypertrophy with a reduced cavity size. While both HCM and CA may demonstrate LV and right ventricular hypertrophy on CMR, their late gadolinium enhancement patterns differ: CA typically exhibits circumferential subendocardial or transmural enhancement, whereas HCM displays patchy mid-myocardial enhancement, especially at the right ventricular insertion points into the septum.^[8] Hypertension-related hypertrophy is generally symmetric, with uniformly hypoechoic myocardium on ultrasound, wall thickness usually ≤ 15 mm, and a septal-to-free-wall ratio < 1.3 . Our patient had a long history of well-controlled hypertension and no family history of HCM. His recent onset of symptoms, unexplained blood pressure normalization, and imaging findings collectively argue against HCM or hypertensive heart disease as the primary cause of his myocardial hypertrophy.

Myocardial hypertrophy may also arise from inherited metabolic disorders, such as iron-overload cardiomyopathy and Fabry disease. While echocardiography in iron-overload cardiomyopathy is non-specific, CMR characteristically shows reduced myocardial signal intensity on T1- and T2-weighted images – the “black heart” sign – with decreased T2* signal being a diagnostic hallmark.^[9] Severe iron overload can lead to myocardial fibrosis, visible as late gadolinium enhance-



ment and elevated extracellular volume on CMR. Our patient exhibited no skin pigmentation, had normal liver function and ferritin levels, and lacked the typical CMR findings, thus ruling out iron-overload cardiomyopathy. Fabry disease commonly presents with symmetric LV hypertrophy and preserved EF. Suggestive echocardiographic clues include the “double-rim sign,” right ventricular hypertrophy, and papillary muscle hypertrophy.^[10] Speckle-tracking echocardiography may show impaired longitudinal strain in the basal inferolateral wall, which carries higher diagnostic value.^[11] On CMR, late gadolinium enhancement in the subepicardial or mid-myocardial basal inferior wall is relatively specific,^[12] while T1 mapping typically demonstrates low native T1 and elevated T2 values, helping to distinguish it from other causes of hypertrophy.^[13] In our patient, despite symmetric LV hypertrophy, neither speckle-tracking nor CMR supported a diagnosis of Fabry disease.

Accurate classification of CA is essential for therapeutic guidance and prognostic assessment. Among the 36 known amyloidogenic proteins, only nine commonly deposit in the myocardium, with AL and ATTR types accounting for over 98% of diagnosed cases. Other types (e.g., AApoAI, AApoAII, AApoAIV, A β 2M, AFib, AGel) are extremely rare, while cardiac amyloidosis (AA type) caused by chronic inflammation and infectious diseases has now also been significantly reduced.^[14] Consequently, clinical typing focuses primarily on distinguishing AL-CA from ATTR-CA. Tc-99m PYP SPECT is a key non-invasive tool for this differentiation, though it carries a risk of false negatives in AL-CA. Thus, concurrent light chain detection during bone scintigraphy is crucial. Twenty-four-hour blood and urine immunofixation electrophoresis (IFE), quantitative serum immunoglobulin, and serum free light chain measurements can achieve diagnostic sensitivity up to 99% for AL-CA.^[15] In our patient, echocardiography and CMR raised suspicion for CA. Tc-99m PYP SPECT was negative, shifting the diagnostic focus toward AL-CA. Serum/urine IFE confirmed a monoclonal IgA- λ protein, and subsequent endomyocardial biopsy revealed Congo red-positive deposits. Immunohistochemistry further demonstrated λ light chain restriction. Together with bone marrow aspiration confirming plasma cell clonality, the patient was ultimately diagnosed with AL cardiac amyloidosis in conjunction with multiple myeloma (MM). In summary, this patient presented with HFpEF as the initial symptom. Following echocardiography and CMR suggesting

CA, differential diagnosis should not only distinguish it from HCM and its phenocopies but also differentiate it from other types of amyloidosis during further subtyping. Subtyping tests include immunopathological staining, immunoelectron microscopy, and mass spectrometry analysis. Genetic testing is also required for suspected hereditary amyloidosis. Furthermore, when diagnosing AL-CA, caution is warranted to differentiate it from other M-protein-associated disorders such as MM, Waldenström's macroglobulinemia, or B-cell lymphoma.

Current standard therapy for AL-CA involves plasma cell-directed regimens analogous to those used in multiple myeloma, including autologous stem cell transplantation (ASCT) for eligible patients. For those with suboptimal responses to conventional regimens, adding a CD38 monoclonal antibody may be considered.^[16] High-dose melphalan with ASCT is generally reserved for younger, fit patients, whereas daratumumab plus lenalidomide and dexamethasone is preferred for elderly or transplant-ineligible individuals.^[17] Volume management—through salt restriction and careful diuretic use—remains the cornerstone of symptomatic care, though close monitoring of blood pressure, fluid balance, and electrolytes is essential given the marked susceptibility to hypotension in these patients.^[16] In our case, following a comprehensive assessment, the patient was deemed unsuitable for ASCT due to advanced age and concerns regarding tolerability. He instead received two cycles of VRD (bortezomib, lenalidomide, dexamethasone) before transitioning to DRd (daratumumab, lenalidomide, dexamethasone) in the third cycle. Throughout treatment, hypotension was managed with rigorous hemodynamic and electrolyte monitoring alongside guideline-directed heart failure therapy. This individualized approach resulted in a favorable hematologic response and stable cardiac function.

DISCLOSURE

Acknowledgements

We sincerely thank Prof. Zheng Zhang for his critical insights and helpful feedback on our manuscript.

Fundings

This study was funded by Gansu Provincial Clinical Medical Research Center for Cardiovascular Diseases (18JR2FA005).



Author contributions

MW and ZZ drafted and critically revised the work, MW and LZ performed language editing, MW and MC performed the literature search and analysis. All authors read and approved the final submission.

Conflict of Interests

The authors declare that there are no conflicts of interest.

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Please cite this article as: WANG MM, ZHANG LX, CHENG MY, ZHANG Z. Unexplained heart failure with preserved ejection fraction diagnosed as amyloidosis of the heart. *J Geriatr Cardiol* 2026; 23(5): 317–321. DOI: 10.26599/1671-5411.2026.05.008

