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Cardiac amyloidosis masked by anchoring bias in a patient with repaired atrial septal defect: a case report

Yan Jiang

342052907@qq.com

Wuhan Asia Heart Hospital

Tian Zhang

Wuhan Asia Heart Hospital

Xiaojing Ma

Wuhan Asia Heart Hospital

Case Report

Keywords: Cardiac amyloidosis, Light-chain amyloidosis, Atrial septal defect, Diagnostic delay, Anchoring bias, Speckle-tracking echocardiography, Case report

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11222509/v1

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Additional Declarations: No competing interests reported.

Abstract

Background: Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy that frequently mimics other cardiac conditions and is easily overlooked once a structural cardiac diagnosis has been established. We report a case of systemic lambda light-chain (AL) amyloidosis unmasked four years after surgical repair of an atrial septal defect (ASD), highlighting the diagnostic anchoring bias that delayed recognition.

Case presentation: A 75-year-old woman presented with refractory heart failure four years after surgical repair of an ASD. Her progressively worsening symptoms had been attributed solely to the pre-existing structural heart disease. On readmission, transthoracic echocardiography demonstrated biatrial enlargement, severe mitral and tricuspid regurgitation, biventricular wall thickening with a granular sparkling appearance, and a small pericardial effusion. Three-dimensional speckle-tracking echocardiography revealed profoundly reduced left ventricular global longitudinal strain (GLS, -6.0%) with relative apical sparing, and reduced right ventricular free-wall longitudinal strain (-8.1%). Electrocardiography showed atrial fibrillation, intraventricular conduction delay, and poor precordial R-wave progression. Serum immunofixation electrophoresis detected a lambda-type monoclonal protein, with a markedly elevated free lambda light chain and a decreased kappa/lambda ratio. Abdominal fat pad biopsy showed Congo red-positive amyloid deposits, and electron microscopy revealed rigid, non-branching amyloid fibrils measuring 8-12 nm in diameter, confirming systemic AL amyloidosis. According to the revised Mayo 2012 staging system (NT-proBNP 29,218 pg/mL), she was classified as stage III. The patient declined bone marrow biopsy and clone-directed chemotherapy and was transferred to another hospital for further management.

Conclusions: Once a structural cardiac diagnosis is established, clinicians are prone to anchoring bias and may overlook coexisting infiltrative disease. In patients with refractory or progressive heart failure after correction of structural heart disease, systematic reassessment-including strain echocardiography, monoclonal protein screening, and tissue biopsy-should be pursued to unmask CA and enable timely, potentially life-prolonging therapy.

Background

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy caused by the extracellular deposition of misfolded protein fibrils in the myocardium and represents a major cause of heart failure with preserved ejection fraction (HFpEF) and unexplained ventricular hypertrophy [1]. Among the nine amyloidogenic proteins known to affect the heart, immunoglobulin light-chain (AL) and transthyretin (ATTR) amyloidosis together account for more than 98% of all CA cases. CA frequently mimics other cardiac conditions, including hypertrophic cardiomyopathy, hypertensive heart disease, valvular disease, and congenital heart disease, and is therefore often misdiagnosed on routine cardiac imaging [2]. Yilmaz et al. [3] reported that approximately one-third of patients with AL amyloidosis consult more than five physicians before the diagnosis is established, and that 37% remain undiagnosed for more than one year after

symptom onset. When a patient has already been diagnosed with a structural cardiac condition, this established diagnosis may further delay the recognition of coexisting infiltrative disease [4, 5].

Over the past decade, substantial advances have been made in CA diagnostic strategies: multiparametric echocardiographic scoring achieves an area under the curve (AUC) of 0.90 for the diagnosis of systemic AL amyloidosis [6]; the combination of serum and urine immunofixation electrophoresis (IFE) with the serum free light-chain (FLC) assay identifies amyloidogenic light chains [7]; and bone scintigraphy enables the non-invasive diagnosis of ATTR cardiac amyloidosis [8]. Nevertheless, tissue biopsy with amyloid typing by immunohistochemistry or mass spectrometry remains the diagnostic gold standard.

We report a 75-year-old woman who presented with refractory heart failure four years after surgical repair of an atrial septal defect (ASD). Despite persistent post-operative symptom progression, her condition had long been attributed solely to the pre-existing structural heart disease. Multimodality imaging, serum monoclonal protein screening, and abdominal fat pad biopsy ultimately established the diagnosis of systemic lambda light-chain AL amyloidosis. This report aims to (1) review the diagnostic pathway and the causes of diagnostic delay; (2) highlight the possibility of coexisting infiltrative cardiomyopathy in patients with structural heart disease; and (3) summarize strategies for the early recognition of suspected CA and the importance of multidisciplinary collaboration.

Case presentation

A 75-year-old woman was admitted to Wuhan Asia Heart Hospital on 10 August 2026 with a 6-month history of chest tightness and dyspnea, accompanied by bilateral lower-extremity edema and orthopnea. Four years prior to this admission, she had presented to another hospital with similar symptoms; transthoracic echocardiography revealed an ASD, and she was diagnosed with heart failure and an ASD. She underwent surgical repair of the ASD in 2022. However, between the operation and the present admission, her chest tightness and dyspnea recurred repeatedly and gradually worsened.

Physical examination on admission: Temperature 36.5°C, pulse 87 beats per minute, respiration 19 breaths per minute, blood pressure 91/65 mmHg. The patient was alert. Coarse breath sounds were heard bilaterally, with decreased breath sounds at bilateral lower lungs. The cardiac rhythm was absolutely irregular. Bilateral lower extremity edema was present. Repeat transthoracic echocardiography demonstrated marked biatrial enlargement, severe mitral and tricuspid regurgitation, interventricular septal and left ventricular wall thickening, and a small pericardial effusion. Three-dimensional speckle-tracking echocardiography revealed biventricular systolic impairment, with markedly reduced left ventricular global longitudinal strain (GLS, -6.0%) and a bull's-eye plot showing the characteristic relative apical sparing pattern, as well as reduced right ventricular free-wall strain, highly suggestive of myocardial amyloid infiltration (Fig. 1a-d). The 12-lead electrocardiogram demonstrated atrial fibrillation, intraventricular conduction delay, poor precordial R-wave progression, left anterior fascicular block, and ST-T changes (Fig. 2).

These findings prompted reconsideration of the underlying etiology of her heart failure-specifically, whether it could be attributable to myocardial infiltrative disease rather than to the structural cardiac abnormality alone. Further serological work-up, including serum immunofixation electrophoresis and a serum free light-chain assay (Table 1), revealed a lambda-type monoclonal protein, a markedly elevated serum free lambda light chain, and a significantly decreased kappa/lambda ratio, providing strong evidence for AL amyloidosis. An abdominal fat pad biopsy was subsequently performed, which showed Congo red-positive amyloid deposits; electron microscopy demonstrated rigid, non-branching amyloid fibrils measuring 8-12 nm in diameter (Fig. 3), establishing the diagnosis of systemic lambda light-chain AL amyloidosis. To evaluate for a potential underlying plasma-cell dyscrasia such as multiple myeloma, bone marrow biopsy was recommended, and hematology referral for clone-directed therapy was advised; however, the patient declined and requested transfer to a comprehensive hospital for further management. After symptomatic treatment for heart failure, she was transferred to another facility for continued care.

Table 1 Laboratory findings on admission

Parameter	Result	Reference range
1. CA staging biomarkers		
N-terminal pro-B-type natriuretic peptide (NT-proBNP)	29,218 pg/mL	<125 pg/mL
High-sensitivity cardiac troponin I (hs-cTnI)	0.1637 ng/mL	<0.0116 ng/mL
Estimated glomerular filtration rate (eGFR)	63 mL/min/1.73 m2	66-143 mL/min
2. Monoclonal protein studies		
Serum immunofixation electrophoresis	lambda-type M protein	Negative
Serum free light chain, lambda	15290.79mg/L	5.71-26.30 mg/L
Kappa/lambda ratio	0.00	0.26-1.65
3. Liver function		
Total bilirubin	22.5 μmol/L ↑	5.0-21.0 μmol/L
Direct bilirubin	5.5 μmol/L↑	0-3.4 μmol/L
Lactate dehydrogenase (LDH)	342 U/L ↑	120-250 U/L
Total protein	59.1 g/L ↓	65-85 g/L
Albumin	37.8 g/L ↓	40-55 g/L
4. Renal function		
Urea	14.03 mmol/L ↑	3.1-8.8 mmol/L
Uric acid	531 μmol/L ↑	155-357 μmol/L
Urea/creatinine ratio	44.0 ↑	12.2-27.9
5. Thyroid function		
Thyroid-stimulating hormone (TSH)	15.33 μIU/mL ↑	0.56-5.91 μIU/mL
Free triiodothyronine (FT3)	2.08 pg/mL ↓	2.3-4.8 pg/mL
Free thyroxine (FT4)	0.88 ng/dL	0.62-1.24 ng/dL

NT-proBNP N-terminal pro-B-type natriuretic peptide; hs-cTnI high-sensitivity cardiac troponin I; eGFR estimated glomerular filtration rate; LDH lactate dehydrogenase; TSH thyroid-stimulating hormone; FT3 free triiodothyronine; FT4 free thyroxine. (up) above reference range; (down) below reference range

Discussion and conclusions

This patient experienced progressive heart failure for four years after ASD repair before CA was ultimately identified at the present admission. Once a definitive structural lesion (ASD) had been

identified, clinicians tended to regard it as the sole cause of her symptoms, overlooking coexisting or newly developed myocardial infiltration; this anchoring bias contributed to the diagnostic delay.

Nitsche et al. [9] reported that 11.8% of 407 elderly patients referred for transcatheter aortic valve replacement had concomitant cardiac amyloidosis (predominantly wild-type ATTR), suggesting that infiltrative cardiomyopathy is not uncommon in older patients with structural heart disease. Only after multimodality re-evaluation did our case exhibit the classic CA imaging phenotype-relative apical sparing on strain imaging, marked reduction in global longitudinal strain (GLS, -6.0%), concomitant right ventricular involvement, and a small pericardial effusion-which redirected the work-up toward monoclonal protein screening and tissue biopsy.

Transthoracic echocardiography in this patient revealed concentric left ventricular wall thickening, a granular sparkling myocardial appearance, marked biatrial enlargement, severe mitral and tricuspid regurgitation, and a small pericardial effusion-findings consistent with the classic CA phenotype. Three-dimensional speckle-tracking echocardiography demonstrated profoundly reduced left ventricular GLS (-6.0%) and right ventricular free-wall longitudinal strain (RVFWSL, -8.1%), consistent with advanced infiltrative disease.

Phelan et al. [10] demonstrated that relative apical sparing identifies CA with a sensitivity of 93% and a specificity of 82%. Yu et al. [4] reported a patient with systemic AL amyloidosis in whom cardiac magnetic resonance (CMR) showed no late gadolinium enhancement and in whom an echocardiographic GLS abnormality (-9.0%) ultimately enabled early recognition-a pattern closely paralleling our patient's GLS of -6.0%. The electrocardiogram in our patient demonstrated atrial fibrillation, intraventricular conduction delay, poor precordial R-wave progression, left anterior fascicular block, and ST-T changes, all concordant with the imaging phenotype [11].

Serum monoclonal protein screening is essential in all patients with suspected CA. In the present case, serum IFE detected a lambda-type monoclonal protein, serum free lambda light chain was markedly elevated, and the kappa/lambda ratio was significantly decreased, providing strong evidence for AL amyloidosis. Subsequent abdominal fat pad biopsy showed 8–12 nm rigid, non-branching amyloid fibrils on electron microscopy with positive Congo red staining, supporting the diagnosis of systemic amyloidosis; however, kappa/lambda immunohistochemistry was not performed on the biopsy specimen.

Quarta et al. [12] demonstrated that abdominal fat pad fine-needle aspiration has a diagnostic sensitivity of 84% in AL cardiac amyloidosis but only 15% in wild-type ATTR, highlighting the importance of type-specific interpretation of biopsy results. When AL amyloidosis is strongly suspected but the fat pad biopsy is negative, endomyocardial biopsy is of decisive value.

AL amyloidosis carries the worst prognosis among all forms of CA. In the present patient, NT-proBNP peaked above 29,000 pg/mL and high-sensitivity cardiac troponin I was persistently elevated; according to the revised Mayo 2012 staging system [13], she was categorized as stage III, indicating a grave

prognosis. Early recognition is critical in AL amyloidosis, as chemotherapy based on CyBorD or Dara-CyBorD significantly improves survival.

Yohannan et al. [14], in a retrospective cohort of 361 patients with AL amyloidosis, validated the ANDROMEDA trial findings: Dara-CyBorD achieved a 6-month hematological very good partial response (VGPR) or better rate of 60.8%, reduced the 6-month mortality rate to 8.8% versus 16.3% (P = 0.04), and yielded superior event-free and overall survival.

Yin et al. [15] reported a patient with Waldenstrom macroglobulinemia complicated by systemic amyloidosis who achieved symptomatic remission after six courses of a bendamustine-rituximab regimen. Our patient, however, was elderly, had concurrent overt hypothyroidism (elevated TSH) and low-T3 syndrome, and declined bone marrow biopsy, precluding clone-directed therapy.

This report has several limitations. As it describes a single case, its generalizability is limited. Moreover, although the diagnostic criteria for cardiac amyloidosis do not strictly require endomyocardial biopsy, the absence of such a biopsy means that coexisting ATTR and AL amyloidosis cannot be entirely excluded on histopathological grounds. In addition, kappa/lambda immunohistochemistry or mass spectrometry-based amyloid typing was not completed on the abdominal fat pad specimen, leaving the diagnosis of AL amyloidosis to be inferred mainly from clinical and serological evidence rather than confirmed at the tissue level.

This case underscores that a diagnosis of structural heart disease should not preclude consideration of coexisting infiltrative cardiomyopathy; patients with refractory or progressive heart failure after surgical or interventional correction warrant systematic reassessment. The combination of relative apical sparing, marked GLS reduction, biatrial enlargement, and pericardial effusion should raise strong suspicion of CA, and monoclonal protein screening (IFE plus the FLC assay with kappa/lambda ratio) should be performed in all patients with HFpEF, unexplained ventricular hypertrophy, or low-voltage electrocardiograms.

Abbreviations

AL: amyloid light chain; ASD: atrial septal defect; ATTR: transthyretin amyloidosis; AUC: area under the curve; CA: cardiac amyloidosis; CMR: cardiac magnetic resonance; CyBorD: cyclophosphamide, bortezomib, and dexamethasone; Dara-CyBorD: daratumumab plus CyBorD; ECG: electrocardiogram; EDV: end-diastolic volume; EF: ejection fraction; eGFR: estimated glomerular filtration rate; ESV: end-systolic volume; FLC: free light chain; FT3: free triiodothyronine; FT4: free thyroxine; GLS: global longitudinal strain; HFpEF: heart failure with preserved ejection fraction; hs-cTnI: high-sensitivity cardiac troponin I; IFE: immunofixation electrophoresis; LDH: lactate dehydrogenase; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RV4CSL: right ventricular four-chamber longitudinal strain; RVFWSL: right ventricular free-wall longitudinal strain; SV: stroke volume; TSH: thyroid-stimulating hormone; VGPR: very good partial response.

Declarations

Trial registration: Not applicable

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Wuhan Asia Heart Hospital (approval no. [to be completed]). Written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

YJ: conceptualization, data curation, investigation, writing-original draft, and writing-review and editing. TZ: investigation, data curation, and visualization. XM: supervision and writing-review and editing. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

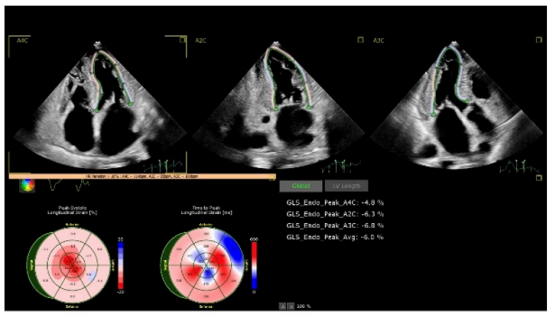
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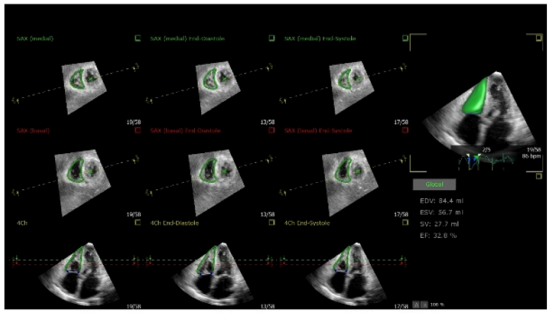
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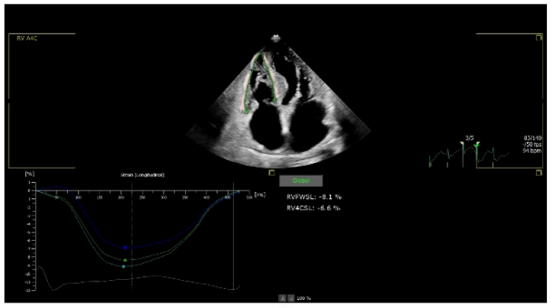
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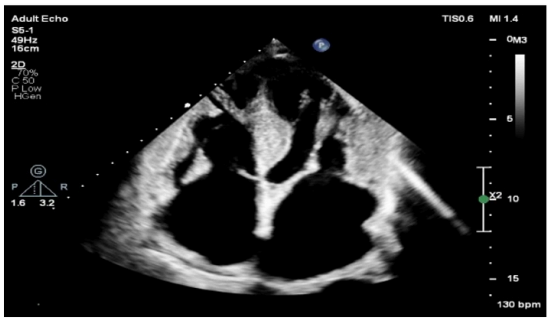
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Figure 1

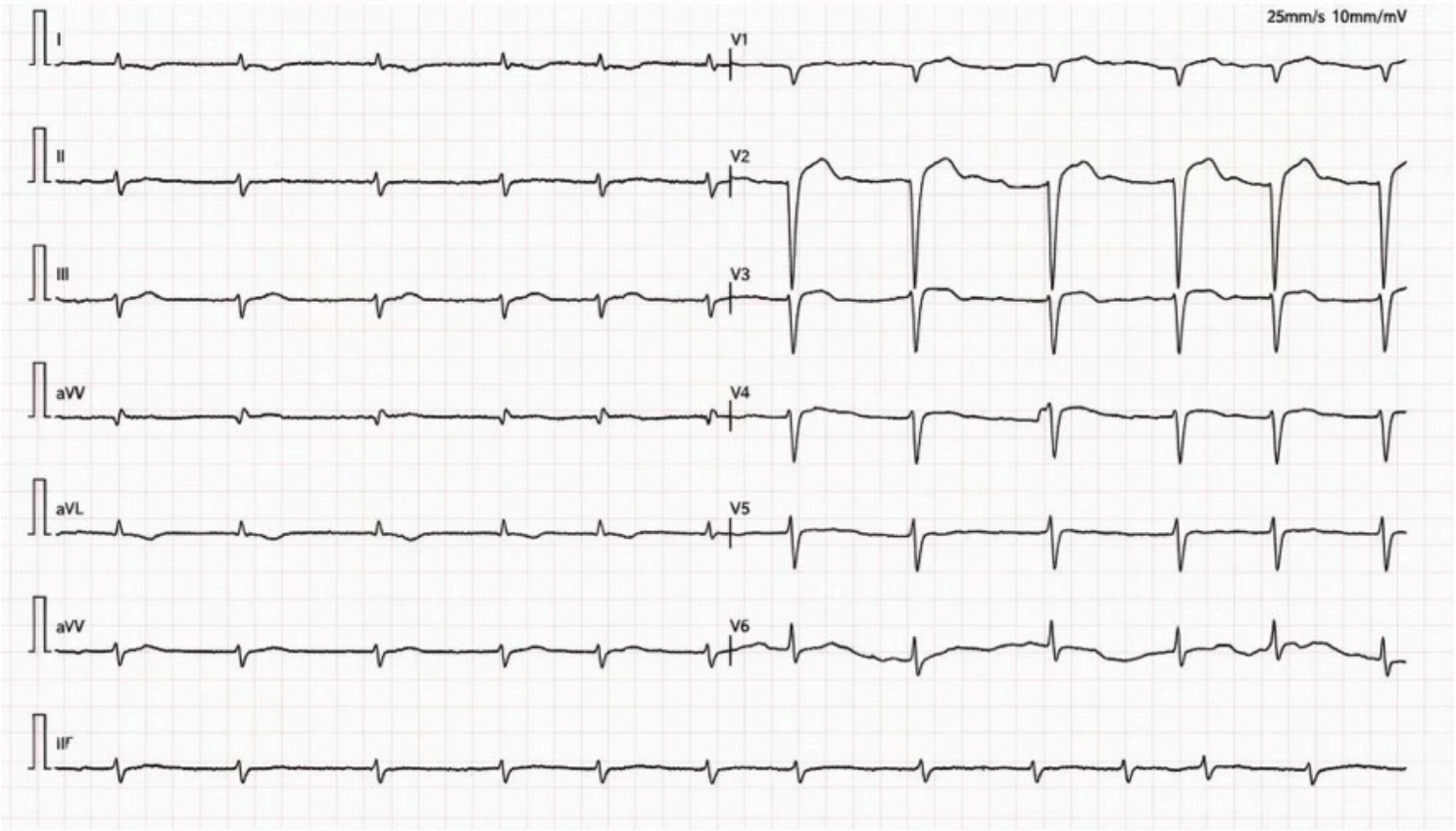


Figure 2

Twelve-lead electrocardiogram demonstrating atrial fibrillation, intraventricular conduction delay, poor precordial R-wave progression, left anterior fascicular block, and ST-T changes.

Supplementary Files

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