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CASE REPORT

CLINICAL CASE

Resolution of Cardiac Infiltration Following Autologous Stem Cell Transplantation for AL Amyloidosis

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ABSTRACT

A 43-year-old man presented with severe heart failure secondary to high-risk light chain cardiac amyloidosis. He underwent chemotherapy and autologous stem cell transplantation with complete hematologic response. Serial cardiac magnetic resonance imaging post-transplant demonstrated gradual normalization of biventricular function and myocardial T_1, a surrogate measure of disease burden. (J Am Coll Cardiol Case Rep 2024;29:102142) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 43-year-old man presented to the emergency department with shortness of breath of 6 months' duration. He previously played ice hockey regularly, but now experienced NYHA functional class III dyspnea. He had no associated chest pain, cough, orthopnea, or paroxysmal nocturnal dyspnea. His blood pressure was 114/82 mm Hg, heart rate was 105 beats/min, and oxygen saturation was 94% on room air. He had jugular venous distention, fine crackles to both bases, an S_3 gallop, and bilateral lower extremity edema to his mid shins.

LEARNING OBJECTIVES

- To understand the management of AL cardiac amyloidosis in a multidisciplinary setting.
- To use serial noncontrast CMR to monitor myocardial amyloid disease burden and response to chemotherapy and stem cell transplantation in patients with AL cardiac amyloidosis.

PAST MEDICAL HISTORY

He was a 15-pack year smoker but otherwise had no prior medical issues and was not taking any medications.

DIFFERENTIAL DIAGNOSIS

His clinical presentation is most consistent with decompensated heart failure. Potential etiologies included ischemic cardiomyopathy, idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, valvular heart

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ABBREVIATIONS AND ACRONYMS

AL = amyloid light chain

ASCT = autologous stem cell transplantation

CMR = cardiac magnetic resonance

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

disease, toxin-induced, metabolic-associated, and nutritional deficiency-related.

INVESTIGATIONS

Blood work showed leukocytosis 12.5 × 10^9/L (normal: 4-11.0 × 10^9/L) and C-reactive protein 21.7 mg/L (normal: <8.0 mg/L). His electrolytes, renal function, and liver profile were normal, including alkaline phosphatase of 78 U/L. Circulating cardiac biomarkers were elevated, N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 11,309 ng/L (normal: <200 ng/L) and high-sensitivity troponin T of 133 ng/L (normal: <14 ng/L). An electrocardiogram revealed sinus rhythm with late R-wave transition and Q waves in the high lateral leads (Figure 1). He was admitted to the hospital for volume management and investigation of new heart failure.

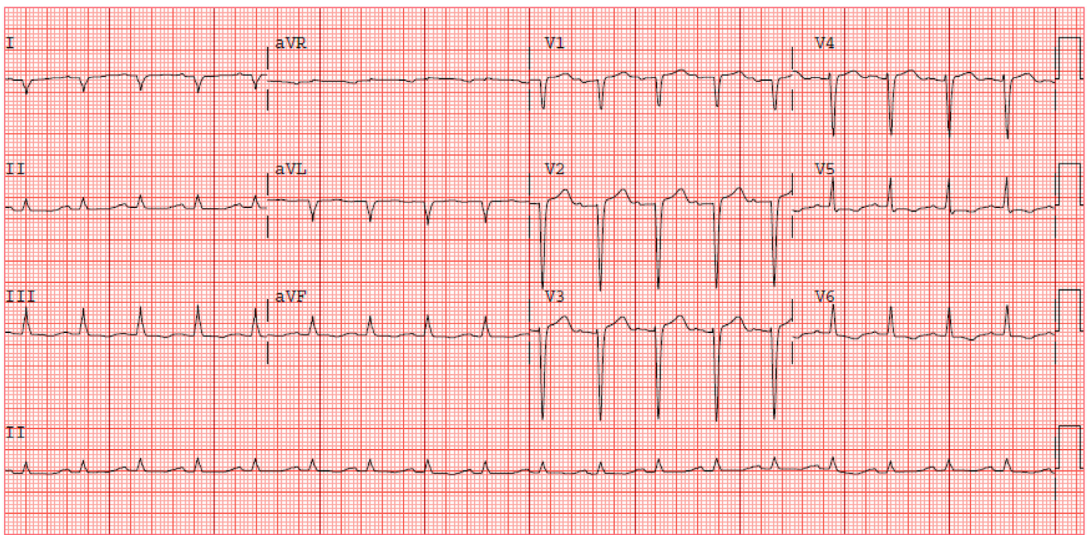
A chest computed tomography found mottled lesions throughout the sternum, ribs, and thoracic spine (Figure 2). Subsequent skeletal survey and bone scan confirmed multiple small osteolytic lesions that are concerning for multiple myeloma. A transthoracic echocardiogram identified severe concentric left ventricular hypertrophy, moderate biventricular dysfunction, and grade 3 diastolic dysfunction. Baseline cardiac magnetic resonance (CMR) imaging found severe biventricular dysfunction, left ventricular ejection fraction (LVEF) of 26% and right ventricular ejection fraction of 26%, increased wall thickness measuring up to 16 mm, and diffuse myocardial late gadolinium enhancement, which was most pronounced in the subendocardium (Figure 3). Serum and urine protein electrophoresis with immunofixation demonstrated a monoclonal band in the β region, elevated serum free κ light chains measured 1,737.6 mg/L (normal: 3.3-19.4 mg/L) with an elevated kappa/lambda ratio of 267.32 (normal: 0.26-1.65). A subsequent bone marrow biopsy found clonal plasmacytosis (kappa light chain expressing) involving 75% of the cellular marrow with Congo red staining present.

He was diagnosed with multiple myeloma (International Staging System stage I) and high-risk Mayo stage III amyloid light chain (AL) amyloidosis with multisystem involvement. His lactate dehydrogenase was 185 U/L (normal: 100-225 U/L), albumin of 40 g/L (normal: 35-50 g/L), and β-2-microglobulin of 3.24 mg/L (normal: 1.00-2.40 mg/L). His cytogenetics showed no evidence of deletion p53 mutation or t(4;14) translocation, and was insufficient for t(14;16) analysis.

MANAGEMENT

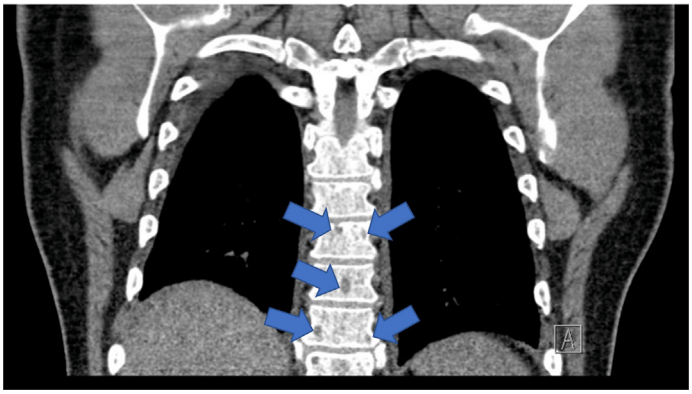
He received 9 cycles of cyclophosphamide, bortezomib, and dexamethasone chemotherapy. After his

FIGURE 1 Baseline Electrocardiogram



Baseline electrocardiogram showing sinus tachycardia with poor R-wave progression, small QRS voltages in the limb leads, Q waves in leads I and AVL, and nonspecific inferolateral T-wave changes.

FIGURE 2 Coronal View From Chest Computed Tomography



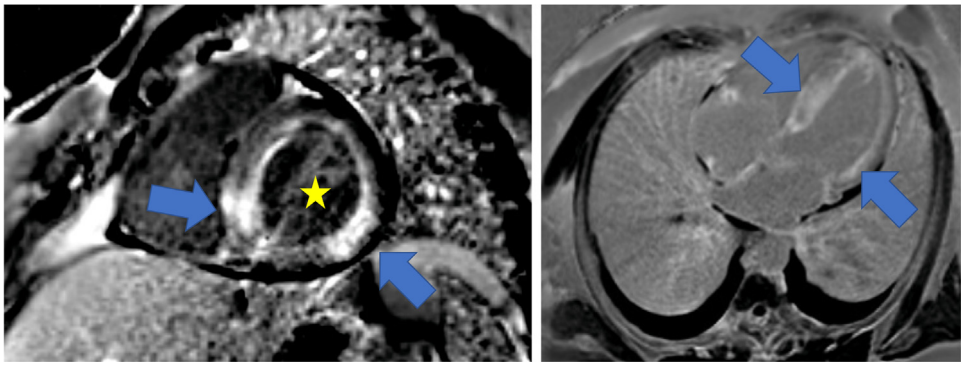
Coronal view from chest computed tomography demonstrating lytic lesions throughout the thoracic vertebrae (blue arrows).

third cycle, his exercise tolerance improved to NYHA functional class II and LVEF increased to 36% on CMR. However, he had evidence of high myocardial amyloid burden with native septal T_1 of 1,180 milliseconds using the modified Look-Locker inversion recovery sequence (normal: <1,040 milliseconds), increased myocardial extracellular volume fraction of 52% ± 9% (normal: <29%), and persistent myocardial late gadolinium enhancement. He received an additional 5 cycles of maintenance bortezomib with improvement of LVEF to 46% on CMR and then underwent melphalan (200 mg/m^2)-conditioned autologous stem cell transplantation (ASCT).

FOLLOW-UP

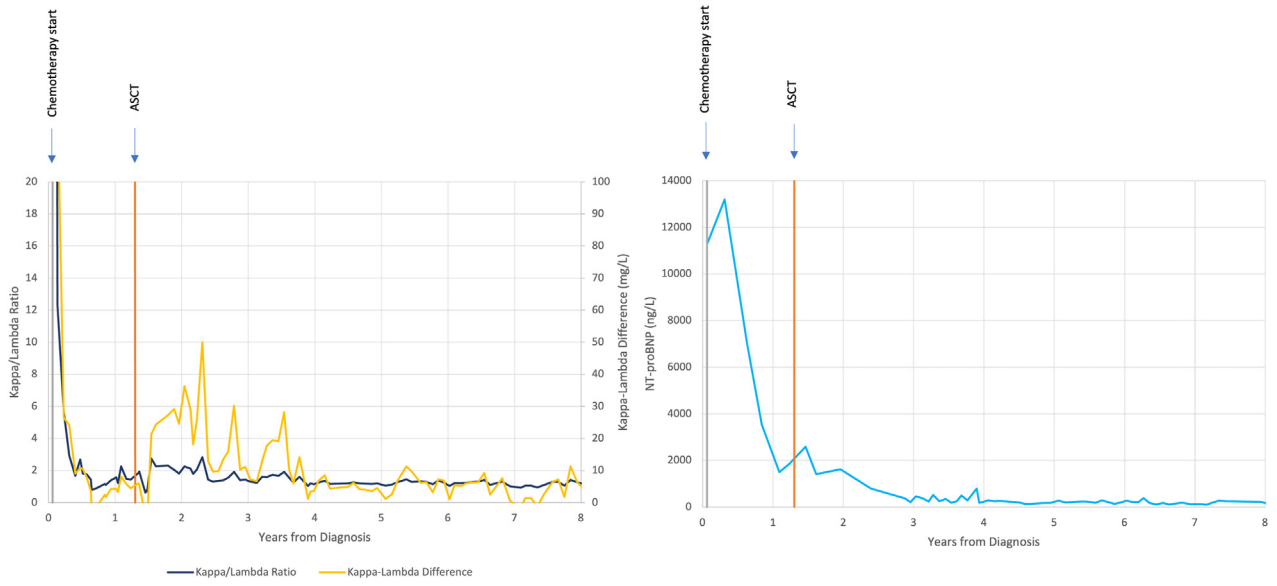
He demonstrated complete hematologic response with normalization of serum free light chains (Figure 4) and absence of monoclonal peak on follow-up serum and urine electrophoresis. He also achieved a significant reduction in NT-proBNP that was consistent with a cardiac response to treatment[1] (Figure 4). Serial CMR follow-up imaging demonstrated gradual improvement (Figures 5 and 6). His exam at 6.5 years from ASCT indicated normalization of cardiac measurements including LVEF of 56%, right ventricular ejection fraction 54% and septal T_1 of

FIGURE 3 Cardiac Magnetic Resonance at Presentation



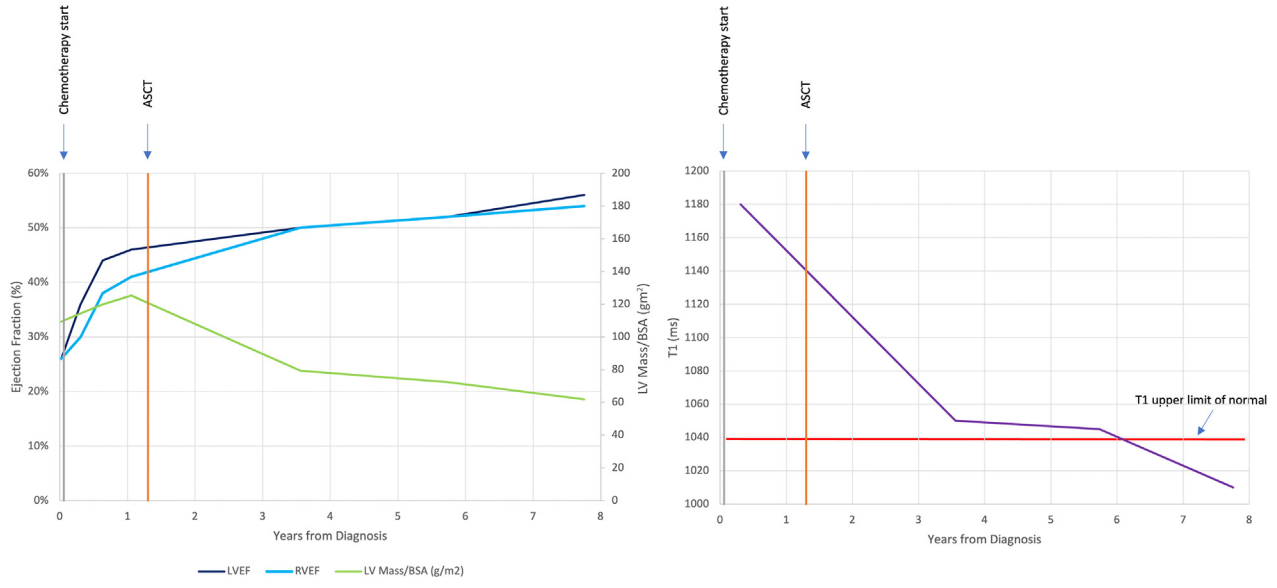
Late gadolinium enhancement imaging demonstrating late blood pool nulling (yellow star) and myocardial late gadolinium enhancement (blue arrows).

FIGURE 4 Temporal Trends in Serum Free Light Chains and NT-proBNP



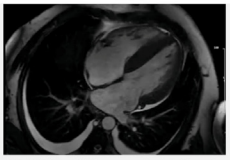
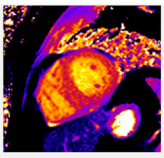
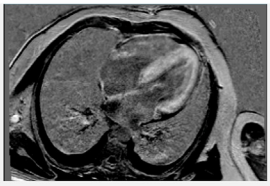
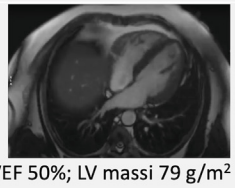
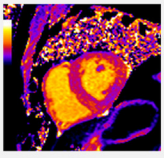
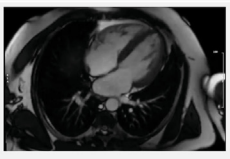
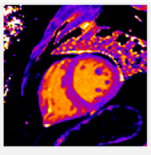
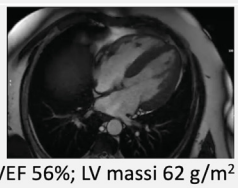
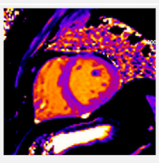
The start of chemotherapy and autologous stem cell transplantation (ASCT) are indicated by the gray and orange vertical lines, respectively. Initial and latest kappa/lambda ratio were 267.3 and 1.35, respectively. Initial and latest kappa-lambda difference were 1,731.1 and 8.8, respectively. Initial and latest N-terminal pro-B-type natriuretic peptide (NT-proBNP) were 11,309 ng/L and 166 ng/L, respectively. Normal values: kappa/lambda ratio: 0.26-1.65; kappa-lambda absolute difference: ≤20; and NT-proBNP: <200 ng/L.

FIGURE 5 Temporal Trends of Cardiac Magnetic Resonance Measures



Left ventricular ejection fraction (LVEF) (black), right ventricular ejection fraction (RVEF) (blue), left ventricular mass indexed to body surface area (LV massi) (green), and native septal T_1 relaxation time (purple). The start of chemotherapy and ASCT are indicated by the gray and orange lines, respectively. Normal values: LVEF: ≥55%; RVEF: ≥50%; LV massi: ≤84 g/m^2; and myocardial T_1: 950-1,040 milliseconds. Abbreviations as in Figures 3 and 4.

FIGURE 6 Follow-Up Cardiac Magnetic Resonance

Time from Autologous Stem Cell Transplant	Steady State Free Precession Cine	Myocardial Native T1	Late Gadolinium Enhancement Imaging
1 year prior	 LVEF 36%; LV massi 114 g/m^2	 T1 1180 ms	
2.25 years post	 LVEF 50%; LV massi 79 g/m^2	 T1 1050 ms	Not Available
4.4 years post	 LVEF 52%; LV massi 72 g/m^2	 T1 1045 ms	Not Available
6.5 years post	 LVEF 56%; LV massi 62 g/m^2	 T1 1010 ms	Not Available

Columns demonstrate LVEF, LV massi, septal myocardial T_1, and late gadolinium enhancement imaging at various times during follow-up. Normal values: LVEF: ≥55%; LV massi: ≤84 g/m^2; and myocardial T_1: 950-1,040 milliseconds. Note that gadolinium was not administered post-transplantation to minimize contrast exposure. Abbreviations as in Figures 3 and 5.

1,010 milliseconds. At 7 years from his ASCT, he reported no heart failure symptoms and feels well on maintenance lenalidomide.

DISCUSSION

Amyloidosis is a rare disorder characterized by systemic extracellular deposition of amyloid fibrils.[1,2] AL amyloidosis usually arises from clonal plasma cell disorders,[2] and 70% of patients will have cardiac involvement.[1,3] Myocardial deposition of amyloid fibrils distorts cardiac architecture and causes direct cardiomyocyte toxicity. Clinically, this myocardial infiltration manifests as cardiac thickening and dysfunction, heart failure, arrhythmias, and adverse clinical outcomes. Prognostication of AL amyloidosis is usually performed using the Mayo staging, which include NT-proBNP, troponin, and difference between free light chains.[1] CMR provides high-definition structural and functional imaging to characterize cardiac involvement using myocardial T_1 mapping and late gadolinium enhancement imaging.[4] Furthermore, noncontrast myocardial T_1 on CMR at baseline is a prognostic marker in patients with systemic AL amyloidosis; a myocardial T_1 >1,044 milliseconds is associated with HR of 5.39 for mortality at a median of 23 months.[5]

The novel aspects of our case include: 1) the dramatic improvement in AL amyloid disease burden with normalization of cardiac parameters during extended follow-up; and 2) the utility of serial noncontrast CMR to monitor the long-term treatment effect. A recent review of 648 patients with AL amyloidosis treated with high-dose melphalan and ASCT found that 39% achieved a complete hematologic response and a median overall survival of

15 years.[6] However, patients with advanced Mayo stage III disease, like our patient, typically do not survive to transplant and have a median survival of 7 months.[7] Similarly, patients with a concurrent diagnosis of multiple myeloma have worse outcomes compared to patients with AL amyloidosis without myeloma (median survival of 13 months vs 31 months).[8,9] Considering the severity of his illness at presentation, our patient had remarkable reduction in his circulating biomarkers with normalization of serum light chains and NT-proBNP at 3 years and normalization of his cardiac function and native myocardial T_1 at 6.5 years from ASCT. His exercise intolerance also resolved, and he has returned to playing ice hockey.

This case demonstrates the potential role of noncontrast CMR for monitoring the long-term treatment response of patients with AL amyloidosis-associated cardiomyopathy. This is the first long-term report of serial CMR following chemotherapy and ASCT for AL amyloidosis with eventual normalization of myocardial T_1. CMR is an attractive option to monitor AL cardiac amyloidosis due to its ability to noninvasively assess amyloid tissue burden.[10]

Currently, no studies address the optimal follow-up scheme for patients with AL cardiac amyloidosis,[1] especially after ASCT. Our case supports the use of serial noncontrast CMR to assess treatment response. Prospective studies evaluating the timing of surveillance imaging and its impact on clinical management and outcomes are needed to enhance the care of patients with this rare disease.

CONCLUSIONS

This case demonstrates the management of AL cardiac amyloidosis including light chain suppression therapies and treatment of concurrent heart failure. In addition to the serial assessment of circulating hematologic and cardiac biomarkers, CMR can be used to monitor treatment response following chemotherapy and ASCT in patients with AL cardiac amyloidosis. Noncontrast myocardial T_1 on CMR evaluates myocardial amyloid disease burden.

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