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NEW-ONSET CARDIAC AMYLOIDOSIS WHILE IN REMISSION FROM SYSTEMIC AL AMYLOIDOSIS

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ABSTRACT

In light chain amyloidosis, a reduction in dFLC to below 40 mg/l is a prerequisite for organ recovery as nearly half of the patients who achieve very good partial haematological responses have improvement in the function of the involved organ. We describe a patient who developed new-onset cardiac amyloidosis despite a post-treatment reduction in dFLC to <10 mg/l.

KEYWORDS

Light chain, plasma cell, cardiac amyloidosis

LEARNING POINTS

- Patients with light chain (AL) amyloidosis may develop new cardiac involvement despite achieving haematological remission.
- In patients with AL amyloidosis, a very good partial haematological response (dFLC <10 mg/l) does not obviate the need for regular cardiac monitoring.

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INTRODUCTION

Cardiac involvement is a major predictor of severe disease and an indicator of poor prognosis in light chain (AL) amyloidosis. Amyloid infiltration of the myocardium reduces myocardial perfusion, disrupts the cardiac conduction system, and is toxic to the myocytes, producing diastolic and systolic dysfunction and an increased risk of arrhythmia[1]. Clinically, this translates to significant morbidity and increased mortality. Hence, it is imperative to evaluate for cardiac involvement at the initial diagnosis of AL amyloidosis. Studies show that a reduction in amyloidogenic serum light chains with plasma cell-directed therapy prevents new cardiac amyloid deposits and may improve involved organ function and patient survival. The goal of plasma cell-directed therapy is to achieve <40 mg/dl dFLC (difference in involved and uninvolved light chains), so-called very good partial haematological response (VGPR). A subset of patients with low levels of involved light chains (<50 mg/dl) at the time of diagnosis need to aim for dFLC <10 mg/dl[2]. This case report details an unusual development of new-onset cardiac amyloidosis in a patient even though they had achieved a haematological VGPR to treatment.

CASE DESCRIPTION

An 82-year-old woman was diagnosed with biopsy-proven renal AL amyloidosis after presenting with nephrotic-range proteinuria (3 g/24 h). Her serum protein electrophoresis revealed 0.7 mg/dl IgG lambda monoclonal protein with a serum lambda (λ) light chain level of 28.3 mg/l (normal: 5.71–26.3 mg/l) and kappa chain 8.6 mg/l (normal: 3.3–19.4 mg/l) with dFLC of 20.6 mg/l. Bone marrow biopsy showed 13% plasma cells with lambda predominance and fluorescent in situ hybridization showed t(11;14), confirming underlying plasma cell neoplasm. Laser mass spectroscopy of the kidney biopsy specimen confirmed AL-λ amyloid. Baseline cardiac troponin-I (cTnI) was 0.01 ng/ml (normal: <0.04 ng/ml), NT-proBNP 393.5 pg/ml (normal: <450 pg/ml), echocardiographic left ventricular ejection fraction (LVEF) 60–65%, and LV global longitudinal strain (GLS) −13.5% (normal: −19 to −22%) with an unremarkable apical sparing ratio (ASR) of 0.46 *(Fig. 1)*, suggesting no cardiac involvement. Due to her age, the patient was not considered a candidate for an autologous stem cell transplant and was initiated on chemotherapy with cyclophosphamide, bortezomib and dexamethasone (CyBorD). Subsequently, her dFLC decreased to <10 mg/l after five cycles of chemotherapy.

Three months after cessation of CyBorD, proteinuria increased to 5.9 g/24 h, and dFLC increased to 21 mg/l. At the time of disease progression, her NT-proBNP was 367 pg/ml, cTnI 0.03 ng/ml, LVEF 65–75%, and GLS was normal at −20% with ASR of 0.8 *(Fig. 2)*, again ruling out cardiac amyloidosis. Daratumumab was initiated as second-line therapy. Proteinuria decreased to 3.9 ng/l and her dFLC declined to 6.7 mg/l after eight cycles of treatment.

Eleven months after the last cycle of daratumumab, the patient presented with new dyspnoea. Her dFLC was still

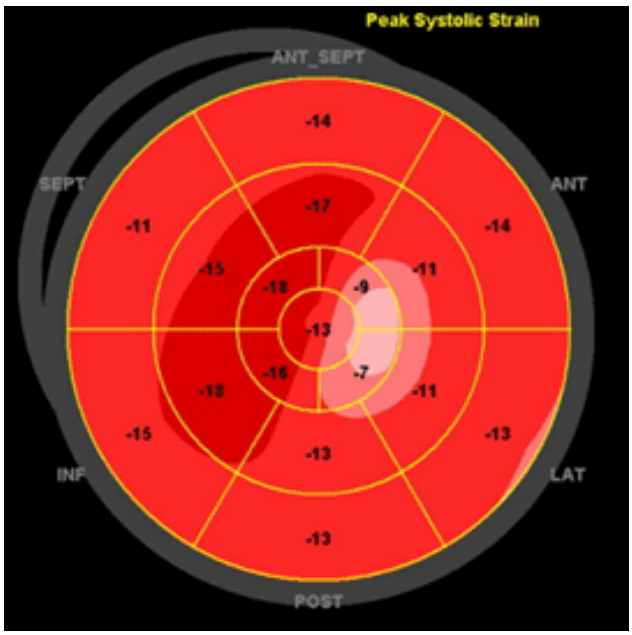

Figure 1. Global longitudinal strain of −13.5% with an apical sparing ratio (ASR) of 0.46 at diagnosis of AL amyloidosis. The ASR and the strain pattern were not suggestive of cardiac amyloidosis

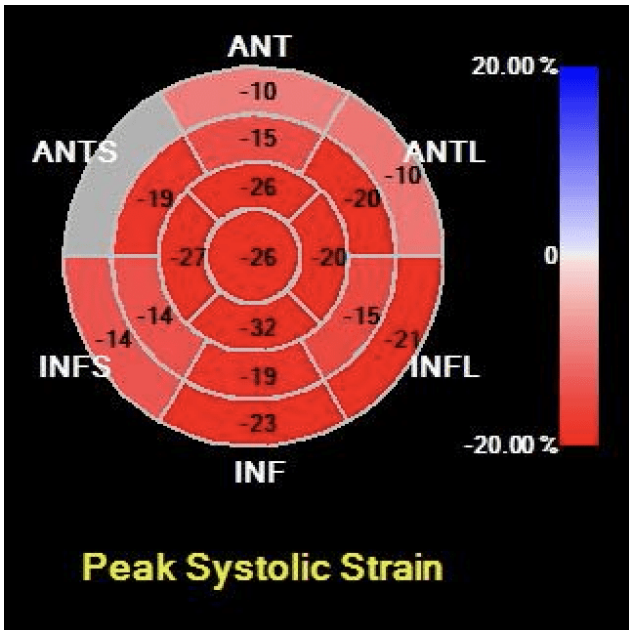

Figure 2. Normal global longitudinal strain of −20% with an apical sparing ratio (ASR) of 0.8 three months after cessation of first-line chemotherapy

<10 mg/l, but NT-proBNP and cTnI were increased to 1,517 pg/ml and 0.06 ng/ml, respectively. LVEF was 70%, an electrocardiogram showed low voltage QRS, and GLS had reduced to −12.2% with ASR 0.96 *(Fig. 3)* and the classic 'cherry on top' bull's eye pattern highly suggestive of cardiac amyloidosis

A Tc-99m-pyrophosphate scan demonstrated a heart/contralateral lung uptake ratio of 1.3, ruling out ATTR amyloidosis. Cardiac MRI showed late gadolinium enhancement (LGE) in a diffuse subendocardial, 'zebra stripe' pattern especially in the apical left ventricle. There was transmural lateral LGE in the mid-left ventricle as well as atrial

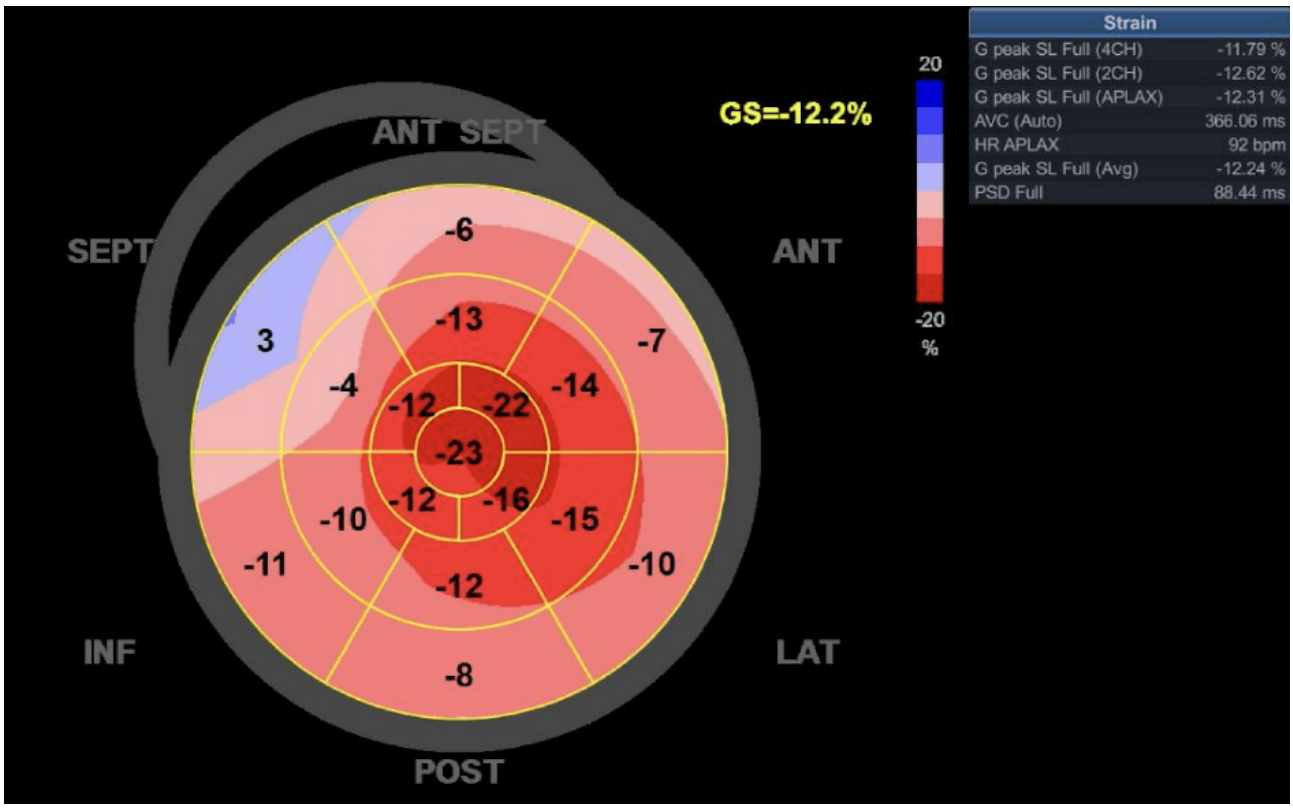

Figure 3. Abnormal global longitudinal strain of −12.2% with an apical sparing ratio (ASR) of 0.96 and the characteristic 'cherry on top' bull's eye image pattern after remission of systemic AL amyloidosis

LGE *(Fig. 4)*, all confirmed cardiac amyloidosis. Nonetheless, a repeat bone marrow biopsy showed neoplastic plasma cells had reduced to 2%. Subsequently, third-line therapy was initiated with venetoclax due to the development of new cardiac amyloidosis despite a haematological VGPR with a goal to achieve minimal residual disease[3].

DISCUSSION

The goal of the management of AL amyloidosis with chemotherapy and autologous stem cell transplant (in select patients) is to mitigate the production of clonal plasma cells and decrease circulating amyloidogenic light chains[4]. Nearly half of the patients who achieve a haematological VGPR or a complete response (negative urine and serum immunofixation with a normalized FLC ratio) also achieved organ response[5]. Close to 20% of patients with AL amyloidosis present with a low light chain burden (pre-treatment dFLC <50 mg/l).

A goal of therapy is to decrease dFLC to <10 mg/l[2]. Regardless of dFLC at the time of diagnosis, decreasing dFLC to <10 mg/l or achieving a complete haematological response correlates with better organ response and overall survival[6].

Our patient had a non-measurable disease burden (baseline dFLC was 20.6 mg/l) and had no cardiac involvement at initial diagnosis as evidenced by the normal strain pattern on echocardiogram. Similarly, she achieved a dFLC response below the desirable 10 mg/l, and the population of the abnormal plasma cells in the bone marrow reduced to 2% after the initiation of chemotherapy. These are evidence of good haematological treatment responses that have been associated with a good prognosis[7]. Despite a haematological VGPR, our patient developed new-onset cardiac amyloidosis based on ASR on speckle tracking echocardiography, which is highly sensitive and specific for detecting cardiac

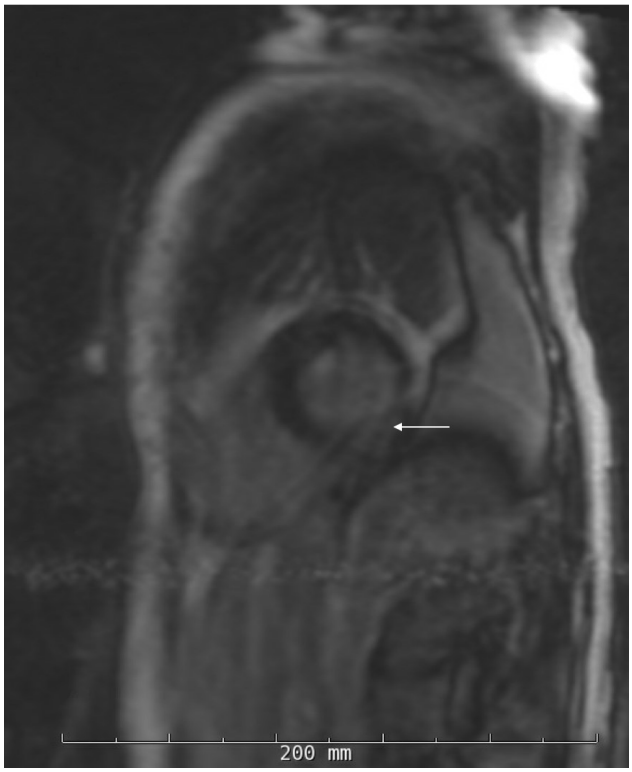

Figure 4. Short-axis late gadolinium enhancement (LGE) protocol on cardiac MRI showing full thickness LGE of lateral and inferolateral myocardium (arrow)

amyloidosis[8]. She also demonstrated abnormalities in cardiac biomarkers such as troponin-I and NT-proBNP with high diagnostic sensitivity for cardiac involvement, and associated with poorer prognosis and decreased survival times[9]. The diagnosis of cardiac amyloidosis was further confirmed on cardiac MRI. Furthermore, the subsequent normal Tc-99m-pyrophosphate scan confidently ruled out transthyretin-related cardiac amyloidosis[10].

New organ infiltration despite the achievement of a reduction in the monoclonal plasma cells and amyloidogenic light chains is not a common pattern for AL amyloidosis. This suggests that the potential for amyloid to infiltrate new organs and consequently cause organ dysfunction could exist even when a patient attains a stringent haematological response (dFLC <10 mg/l). These patients may benefit from additional treatment to achieve a minimal residual disease state[3].

Physicians are therefore reminded of the quintessential need for routine monitoring of the heart with echocardiographic strain measurement, cardiac troponin, and NT-proBNP in all patients with AL amyloidosis, including those with a haematological VGPR.

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