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CASE REPORT

BEGINNER

CLINICAL CASE

Cardiac Amyloidosis

The Importance of Surveillance in a Patient With an Initial Negative Cardiac Biopsy

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ABSTRACT

Cardiac amyloidosis is a progressive disorder and is sometimes difficult to diagnose even when suspected in the appropriate clinical setting. We present an interesting case of rapidly progressive light-chain cardiac amyloidosis and highlights the importance of close monitoring even when the initial biopsy and imaging findings are not pathognomonic for amyloidosis. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:282–5)

HISTORY OF PRESENTATION

A 48-year-old female patient was referred to exclude cardiac amyloidosis (CA). The patient was asymptomatic from a cardiac perspective. Results of general physical and systemic examinations were unremarkable.

PAST MEDICAL HISTORY

The patient was diagnosed with monoclonal gammopathy of unknown significance (MGUS) 6 years earlier. In addition, she was evaluated for recent onset of numbness in both hands. The patient was detected to have bilateral carpal tunnel syndrome, and conservative management was advised.

LEARNING OBJECTIVES

- Recognize the importance of close surveillance in the presence of red flags suggesting CA, even when the initial biopsy and imaging findings are not diagnostic.
- Recall the clinical course and prognosis of AL amyloidosis.

INVESTIGATIONS

Laboratory investigations revealed a cardiac troponin T level of 36 ng/l (normal: <30 ng/l) and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) value of 1,015 ng/l (normal: <125 ng/l). The concentration of serum free light chains was 985 mg/l for the kappa isotype (normal: 3 to 19 mg/l) and 10 mg/l for the lambda isotype (normal: 6 to 26 mg/l). The kappa-to-lambda ratio was 98.5 (normal: 0.26 to 1.65). Although kappa light chains were elevated, they had been stable over the past 6 years, with normal renal function and serum calcium values. A comprehensive work-up for multiple myeloma was negative. A bone marrow biopsy was consistent with MGUS (plasmacytosis of 9%). A rectal biopsy showed no deposits of amyloid. Echocardiographic evaluation revealed a mild increase in left ventricular wall thickness (involving the basal inferior and basal inferolateral walls; maximum thickness of 13 mm)

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Informed consent was obtained for this case.

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with normal left ventricular function. Cardiac magnetic resonance (CMR) confirmed the increased wall thickness, and the time of inversion scout sequence showed a normal pattern of myocardial nulling. Phase-sensitive inversion recovery late gadolinium enhancement imaging demonstrated subepicardial hyperenhancement in the basal inferior and inferolateral segments. In addition, there was hyperenhancement of the left atrial and right ventricular free walls (Figures 1A and 1B). The CMR features raised the suspicion of CA. A right ventricular endomyocardial biopsy (6 samples from the region of the right ventricular septum) showed diffuse interstitial fibrosis with no evidence of amyloid deposition (Figures 1C to 1F). The Congo red-stained biopsy samples did not demonstrate apple-green birefringence on polarized microscopy. The immunoperoxidase studies showed lack of positive labeling with antibodies to amyloid A protein, amyloid P protein, and transthyretin (ATTR). A working diagnosis of idiopathic nonischemic cardiomyopathy was considered, and the patient was monitored closely.

FOLLOW-UP. At 9-month follow-up, clinical features of congestive cardiac failure developed in this patient. Blood investigations showed a cardiac troponin T level of 290 ng/l and an NT-proBNP value of 34,888 ng/l. The concentration of serum free light chains was 1,105 mg/l for the kappa isotype and 6 mg/l for the lambda isotype. The kappa-to-lambda ratio was 184.17. Echocardiography revealed a marginal increase in left ventricular wall thickness (basal septal thickness of 15 mm) with obvious features of grade II left ventricular diastolic dysfunction. Repeat CMR showed a reversed nulling pattern on the time of inversion scout sequence. Phase-sensitive inversion recovery late gadolinium enhancement imaging exhibited extensive subendocardial hyperenhancement circumferentially, involving both the ventricles and the left atrial wall, consistent with CA (Figures 2A and 2B). A subsequent right ventricular endomyocardial biopsy confirmed the diagnosis of CA (light-chain [AL]) (Figures 2C to 2F). The amyloid fibrils stained by Congo red showed apple-green birefringence in polarized light. The immunoperoxidase studies showed a strong positive labeling for antibodies to amyloid P protein and an

ABBREVIATIONS AND ACRONYMS

AL = light-chain

ATTR = transthyretin

CA = cardiac amyloidosis

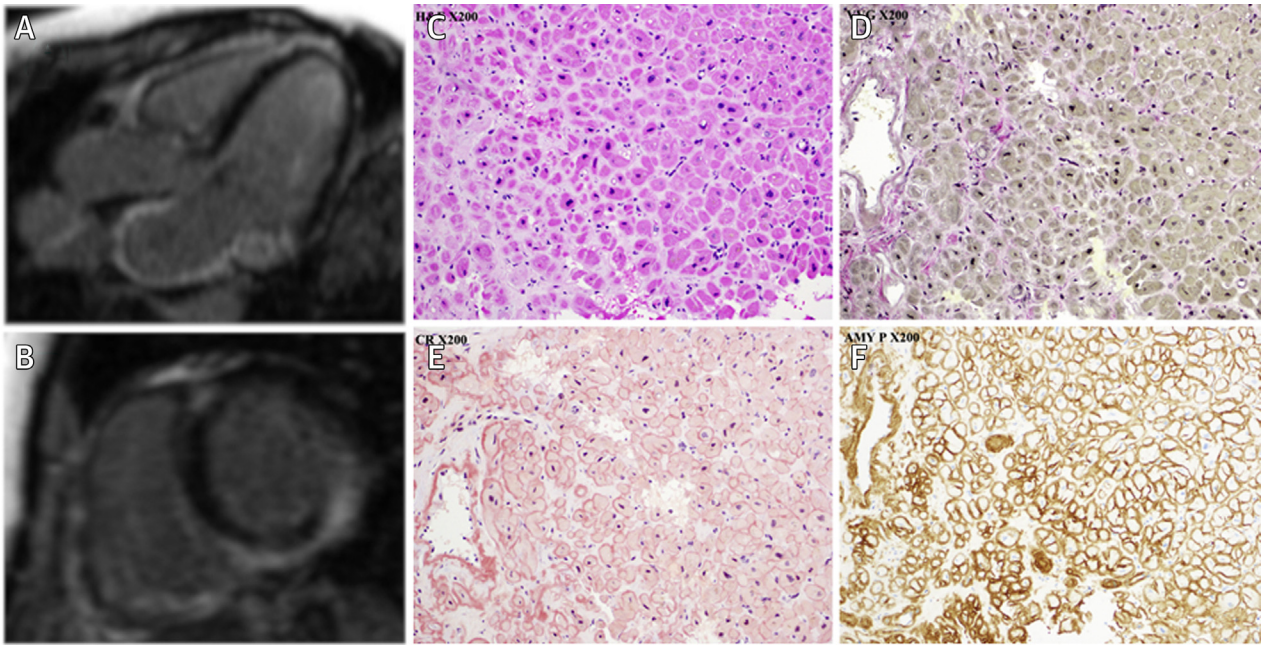
CMR = cardiac magnetic resonance

ECV = extracellular volume

MGUS = monoclonal gammopathy of unknown significance

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

FIGURE 1 Initial CMR Imaging and Right Ventricular Endomyocardial Biopsy



(A and B) Cardiac magnetic resonance (CMR) imaging: long-axis and short-axis views showing subepicardial late gadolinium enhancement involving the basal inferior and basal inferolateral segments of the left ventricle. In addition, there is hyperenhancement of the left atrial and right ventricular free walls. **(C to F)** Right ventricular endomyocardial biopsy samples demonstrating diffuse interstitial fibrosis and no evidence of amyloid deposition. **(C)** Hematoxylin and eosin (H&E) stain. **(D)** Elastic Van Gieson (VVG) stain. **(E)** Congo red (CR) stain. **(F)** Amyloid P immunoperoxidase (AMY P) stain.

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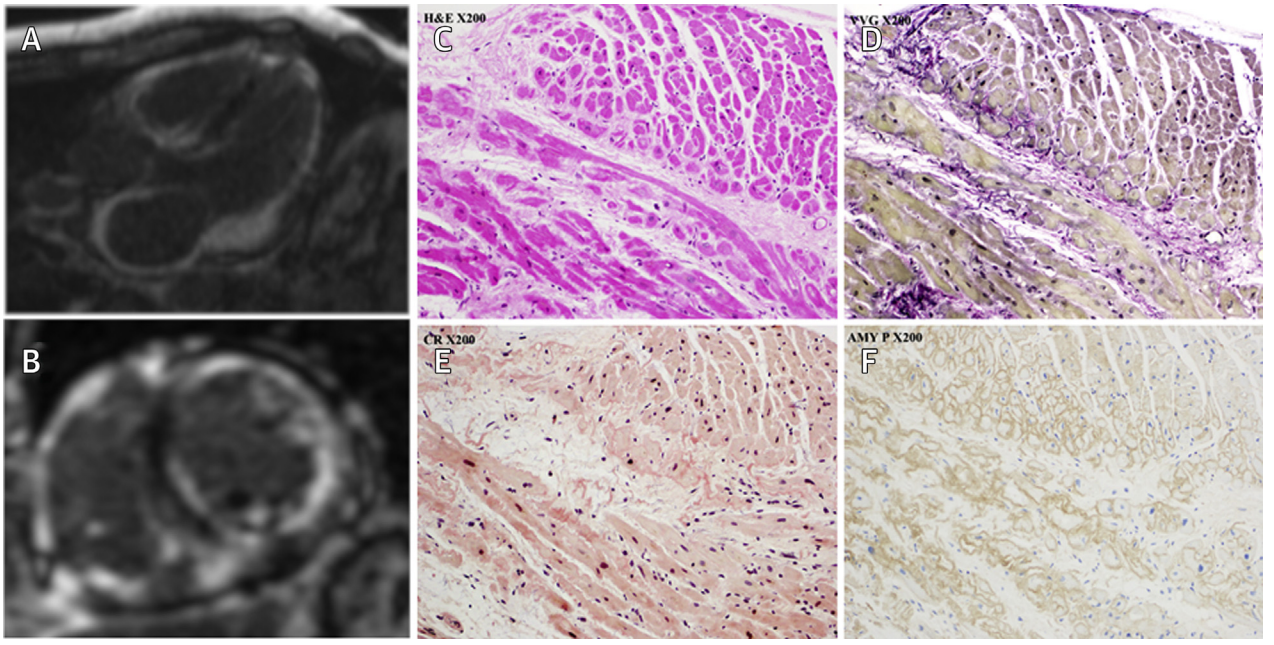
FIGURE 2 Repeat CMR Imaging and Right Ventricular Endomyocardial Biopsy at 9 Months



(A and B) Cardiac magnetic resonance (CMR) imaging: long-axis and short-axis views illustrating global subendocardial late gadolinium enhancement involving both the ventricles and the left atrial wall. **(C to F)** Right ventricular endomyocardial biopsy samples highlighting diffuse amyloid deposition. **(C)** Hematoxylin and eosin (H&E) stain. **(D)** Elastic Van Gieson (VVG) stain. **(E)** Congo red (CR) stain. **(F)** Amyloid P immunoperoxidase (AMY P) stain.

absence of labeling for antibodies to amyloid A protein and ATTR. Bone marrow biopsy revealed an increase in plasma cells (15%) consistent with plasma cell dyscrasia.

MANAGEMENT

The patient was started on anti-heart failure medications and chemotherapy. She required an implantable cardioverter-defibrillator for documented ventricular fibrillation. However, the patient had a progressive downhill course with intractable heart failure and died 6 months later.

DISCUSSION

CA is usually a progressive disorder resulting in early mortality secondary to congestive cardiac failure and arrhythmias. Systemic AL amyloidosis and ATTR amyloidosis are the clinically relevant forms of amyloidosis affecting the heart. These 2 forms of amyloidosis have differing clinical courses, therapies, and prognosis. A delay in establishing a diagnosis is among the factors responsible for poor outcomes. However, as illustrated by our case, this condition, even when suspected, is sometimes challenging to diagnose. In our case, although efforts were made for an early definitive diagnosis, both the initial CMR and the first endomyocardial biopsy were not diagnostic and returned a yield of nonspecific nonischemic cardiomyopathy. However, as is often typical of CA of the AL type, the clinical course was rapidly progressive, and the patient's disorder was eventually diagnosed 9 months later on the basis of both CMR and endomyocardial biopsy. AL amyloidosis has a poor long-term prognosis in comparison with ATTR amyloidosis. The median survival from the onset of heart failure in AL amyloidosis is 6 months. Therefore, given the high mortality in AL amyloidosis, it is imperative to avoid a misdiagnosis or a delay in establishing the diagnosis. CA is generally considered a diffuse myocardial process, but patchy involvement is not uncommon, thus leading to an initial negative endomyocardial biopsy result (1). The diagnosis of CA on CMR is based on the characteristic late gadolinium enhancement pattern (global subendocardial or transmural

hyperenhancement). Native T_1 mapping has emerged as a useful CMR parameter in the assessment of patients with suspected CA. In a recent study by Baggiano et al. (2), the utility of noncontrast CMR (1.5-T clinical scanner, Aera, Siemens Healthcare, Erlangen, Germany) for the diagnosis of CA was evaluated. The native T_1 images were acquired using the modified Look-Locker inversion recovery sequence. A native T_1 >1,164 ms was associated with a 98% positive predictive value for the diagnosis of CA (2). In addition, T_1 mapping (pre- and post-contrast) can also be used to estimate the myocardial extracellular volume (ECV) fraction. The ECV fraction is a surrogate marker to quantify the burden of CA. CA is associated with a higher ECV fraction (46.6 ± 7.0%) than any other cardiomyopathy because of the widespread extracellular deposition of amyloid fibrils (3).

CONCLUSIONS

The diagnosis of CA can be difficult, and CA is often an underdiagnosed cause of heart failure. The diagnosis cannot be solely based on a single imaging modality; rather, a multiparametric assessment (biomarkers, imaging, and tissue biopsy) is necessary for an early and prompt diagnosis. In the appropriate clinical setting (history of MGUS and carpal tunnel syndrome), as highlighted, close monitoring and imaging surveillance are recommended even when the initial biopsy and CMR results are not pathognomonic for CA.

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KEY WORDS amyloidosis, biopsy, cardiac magnetic resonance