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Case Report

Cardiac amyloidosis: A diagnostic challenge ☆

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ABSTRACT

Cardiac amyloidosis is indeed a condition characterized by the deposition of amyloid proteins in the myocardium, leading to thickening and stiffening of the heart muscle. These abnormal protein deposits can interfere with the heart's normal functioning and may pose diagnostic challenges due to its varied clinical presentation and resemblance to other heart condition. Here, we present a case of 55-year-old female patient of uncontrolled hypertensions for 15 years. About 15 years ago, she presented with chest pain and was diagnosed with cardiomyopathy (CM) characterized by low left ventricle (LV) function of unknown cause. Despite being on antihypertensive treatment, the patient continued to experience chest heaviness with persistent elevate blood pressure. An echocardiogram revealed increased LV septal wall thickness, valvular thickening, and biatrial dilation. Subsequently, cardiac magnetic resonance imaging (CMR) was performed, which revealed left atrium enlargement and asymmetrical myocardial wall thickening, particularly at the septum. White blood axial image revealed thickened inter atrial septum, while late gadolinium enhancement (LGE) magnetic resonance (LGE MR) images showed patchy LGE at the base relative to the apex of the myocardium, highlighting the base-to-apex gradient, subendocardial pattern enhancement at apical lateral wall, and transmural pattern enhancement of the mid anteroseptal and inferoseptal wall. Additionally, a short axis time to invert T1 scout image of left ventricle displayed an abnormal nulling pattern initially in the myocardium, followed by the blood pool, and finally the spleen. These findings collectively led to the diagnosis of cardiac amyloidosis.

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Introduction

Amyloidosis is a rare heterogeneous group of disorders characterized by extracellular deposition of abnormally folded proteins, called amyloid, in one or more of the body tissues, finally leading to organ dysfunction with bad prognosis if it is detected in late stages, especially with cardiac involvement [1,2]. The 2 commonest forms of amyloidosis are 1) transthyretin amyloidosis (ATTR), which derived from wide-type or mutant transthyretin, and 2) light-chain (AL) amyloidosis, which derived from abnormal circulating light chain produced by plasma cell dysplasia. Both types frequently involve the heart producing an infiltrative cardiomyopathy (CM) with restrictive pathophysiology [2]. ATTR can be inherited as autosomal dominant (AD) trait caused by pathogenic variants in the transthyretin gene *TTG* (ATTTv) or by the deposition of wide-type transthyretin protein (ATTRwt), previously called senile cardiac amyloidosis. Echocardiography (Echo) offers clues that prompt further testing. Cardiac magnetic resonance (CMR) imaging may indicate an infiltrative process. ^{99m}Technetium (^{99m}Tc) bone-avid compounds represents a paradigm shift and allow the noninvasive diagnosis of ATTR-cardiomyopathy (ATTR-CM) [3].

In this report, we presented a rare case of cardiac amyloidosis which presented with 15 years history of heart disease with no clear diagnosis. The case forming a diagnostic challenge for years, however, CMRI features were the key to pick up the diagnosis. The case report highlights the role of medical imaging using CMR in diagnosis of rare diseases like this case.

Case presentation

A 55-year-old female patient of a history of longstanding uncontrolled hypertensions spanning 15 years presented with ongoing symptoms. Fifteen years prior, she sought medical attention due to chest pain and was diagnosed as CM with low left ventricle function of unknown etiology. The patient blood pressure remains uncontrolled (BP=160/90mmHg) with chest heaviness despite receiving antihypertensive treatment. An echocardiogram was performed, revealing increased LV septal wall thickness, biatrial dilation, and valvular thickening (Figs. 1A-C). An ongoing cardiac involvement despite treatment for hypertension was suggested and warranting further evaluation and management.

Recently, the patient underwent CMR which revealed left atrium enlargement and asymmetrical myocardial wall thickening, particularly at the septum (Fig. 2A). Additionally, a chamber view steady-state free precession image showed a thickened left ventricular wall with trabeculation and preserved cavity volume (Fig. 2B). The interventricular septum was thickened on white blood axial image (Fig. 3A), and T2-diffusion weighted 4 chamber view with no evidence of hypersignal intensity of myocardial wall (Fig. 3B). Late gadolinium enhancement magnetic resonance (LGE MR) images displayed patchy late gadolinium enhancement (LGE) at the base relative to the apex of the myocardium, emphasizing the base-to-apex gradient. Notably, there was diffuse enhancement of the biatrial walls and subendocardial pattern enhancement at most the ventricular myocardium especially apical lateral wall and transmural pattern enhancement of the mid anteroseptal and inferoseptal wall (Fig. 4). Furthermore, a short axis time to invert T1 scout image of left ventricle exhibited an abnormal nulling pattern. Initially, both the blood pool, myocardium, and spleen appeared bright (Fig. 5A). Subsequently, the myocardium nullified before the blood pool (Fig. 5B), followed by nulling of the blood pool (Fig. 5C), and finally the spleen (Fig. 5D). Based on these findings, a diagnosis of cardiac amyloidosis was established.

Follow up, the patient continues with Nouractone 25 mg 1×1, Atoris 20 mg 1×1, Carvediolol 12.5 mg 1/2×2, Alsin 100 mg 1×1, Diatamb 10 mg 1×1, Sacopluse 24/26 1×1 drugs and close flow up of cardiac function by echo.

Discussion

ATTR-CM is a life-threatening progressive infiltrative disease and can often be overlooked as a cause of heart failure. Insufficient awareness of this condition among healthcare providers can result in delayed diagnosis and, consequently, a grim prognosis. Conversely, early detection significantly enhances patient outcomes, emphasizing the critical importance of raising disease awareness for prompt intervention and improved prognosis.

Screening for ATTR-CM in each practice is recommended in the presence clinical scenarios and red flags for ATTR-CM [4]. Our patient was diagnosed as CM presenting low left ventricle function of unknown cause for 15 years. After this duration, the patient underwent echo which demonstrated increased left ventricular septal wall thickness, biatrial dilation, and valvular thickening. A previous study reported that the increased wall thickness (IWT) score derived from echo measurements has good diagnostic performance in diagnosing ATTR-CM (IWT score$\geq$8) with 85.7% sensitivity, and 92.6% specificity, and in excluding ATTR-CM (IWT score$<$5). Echo is an excellent imaging modality for screening and guiding further testing of cardiac amyloidosis [5].

In our patient, CMR revealed left atrium enlargement and asymmetrical myocardial wall thickening particularly at the septum. Chamber view steady state free precession image reveals a thickened left ventricular wall, trabeculated with preserved cavity volume. These findings are typical of ATTR-CM as reported by Martinez-Naharro et al. who noted that asymmetrical hypertrophy, traditionally associated with CM is the commonest pattern of ATTR remodeling [6]. Cine MRI is the standard imaging modality for the assessment of myocardial structure and function, clearly showing regions of asymmetric wall thickening typical for hypertrophic-CM. Furthermore, Cine MRI allows differentiation of hypertrophic-CM from other hereditary disorders such as Fabry disease or transthyretin cardiac amyloidosis, that produce concentric hypertrophy for which CMR is the imaging modality of choice [7].

In our patient, LGE MR images show different kinds of enhancement, patchy late gadolinium enhancement (LGE)

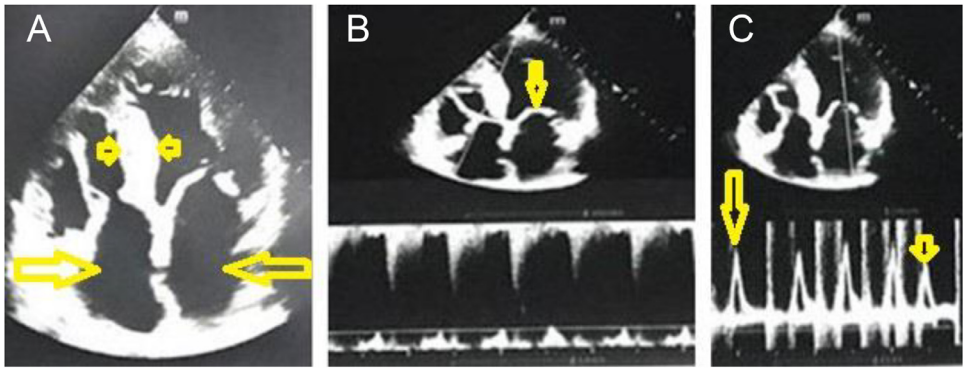

Fig. 1 – Echocardiography selected images (A and B) 4-chamber views showing increased LV septal wall thickness (arrow head on [A]), biatrial dilation (thick arrows on [A]), and valvular thickening are shown (arrows on [B]). (C) Pulsed wave Doppler of the mitral inflow: Mitral inflow demonstrates a high E-wave velocity (long arrow) with a small A-wave velocity, E/A >2, and short deceleration time of 100 msec (short arrow).

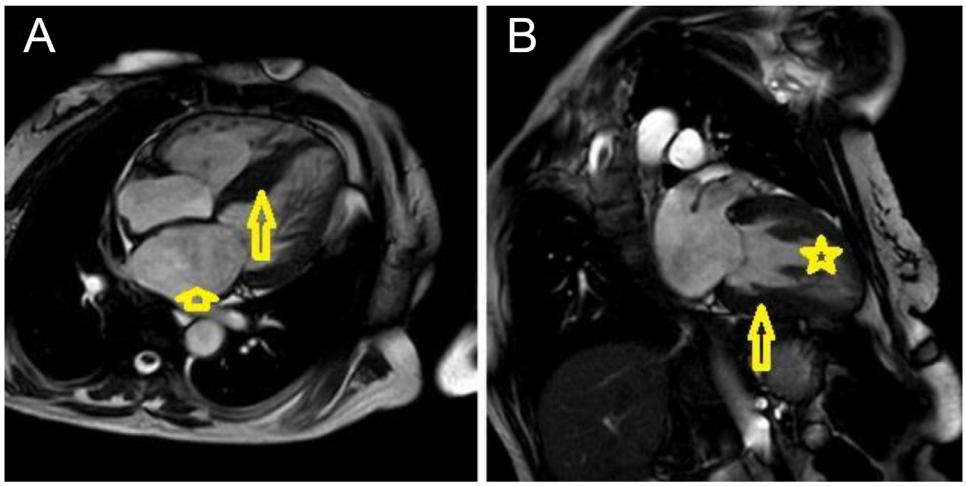

Fig. 2 – 4CH (Chamber view) steady state free precession image reveals: (A) left atrium enlargement (small arrow) and asymmetrical myocardial wall thickening particularly at the interventricular septum (arrow), (B) 2 CH (chamber view) steady state free precession image reveals left ventricular thick wall (arrow), trabeculated (star) with preserved cavity volume.

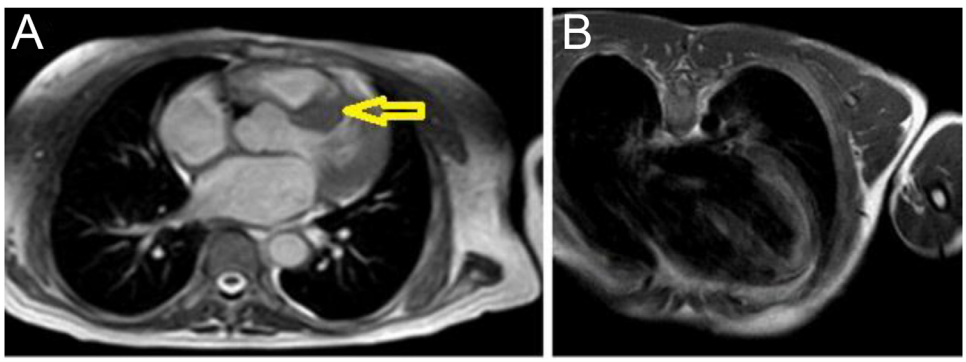

Fig. 3 – (A) White blood axial image shows thickened inter atrial septum (arrow), (B) T2 4 chamber view with no evidence of hypersignal intensity of myocardial wall.

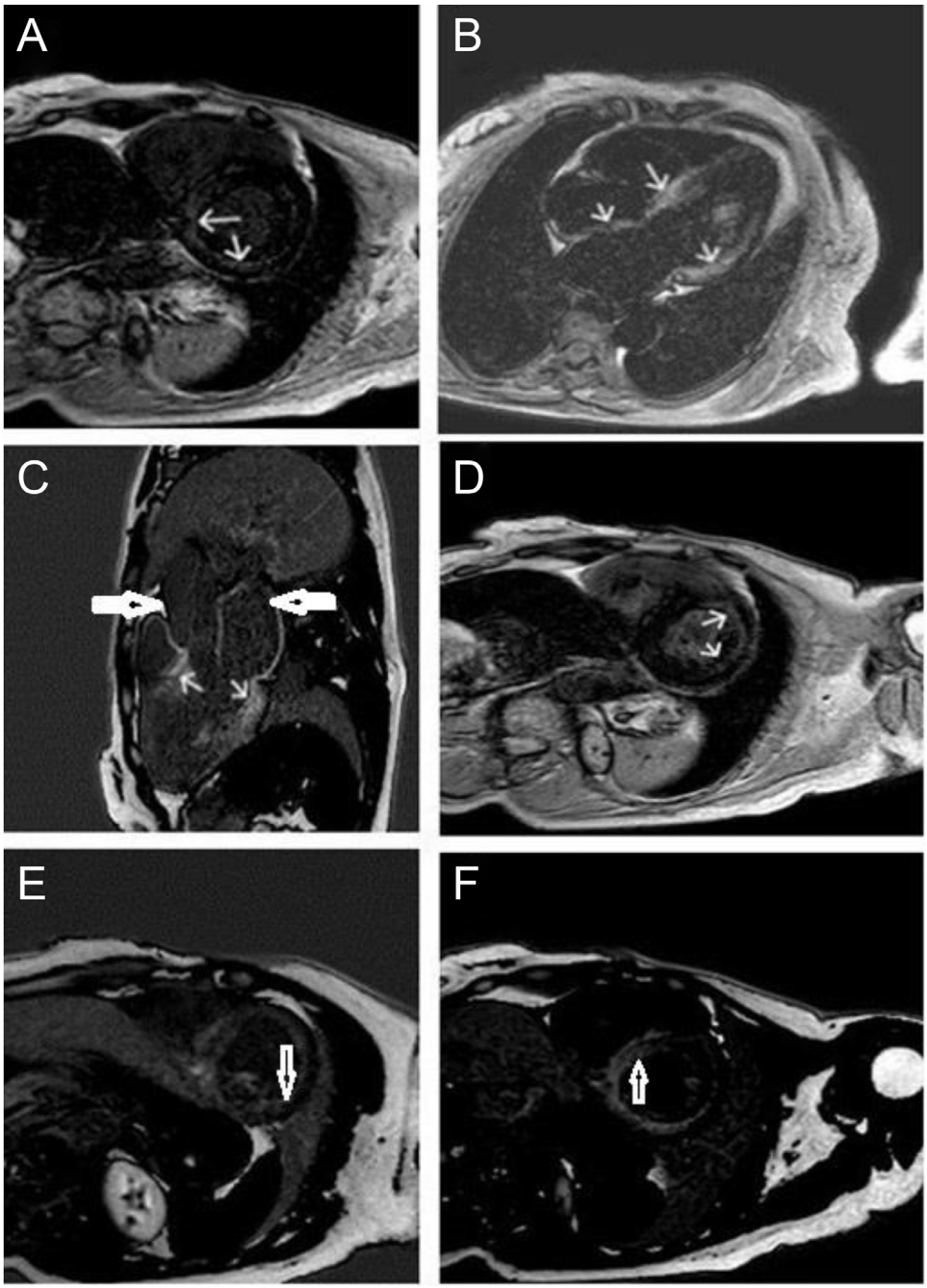

Fig. 4 – LGE MR image (3 -chamber LV out flow (C), short axis views (A, D) and 4-chamber view (B) show patchy late gadolinium enhancement at the base relative to the apex of the myocardium, highlighting the base-to-apex gradient (arrows). In addition, there is diffuse enhancement of both atrial wall (C large arrows). In many parts. the enhancement is subendocardial, most pronounced on (E) short axis subendocardial pattern enhancement at apical lateral wall, (F) short axis view small focal transmural pattern and additional areas of subendocatdial enhancement of mid anteroseptal and inferoseptal wall.

greater at the base relative to the apex of the myocardium. The enhancement was transmural and subendocardial in other parts. This finding is consistent with a previous study that reported extensive LGE in 90% of ATTR compared to 37% of AL patients, and right ventricle LGE in 100% of ATTR compared to 72% of AL patients [8]. A global subendocardial enhancement pattern, which may be transmural or patchy have also reported in other papers [7]. LGE in CMR has proven as a robust and reliable risk marker of adverse outcomes in cardiovascular diseases of different origin. LGE should be offered in the

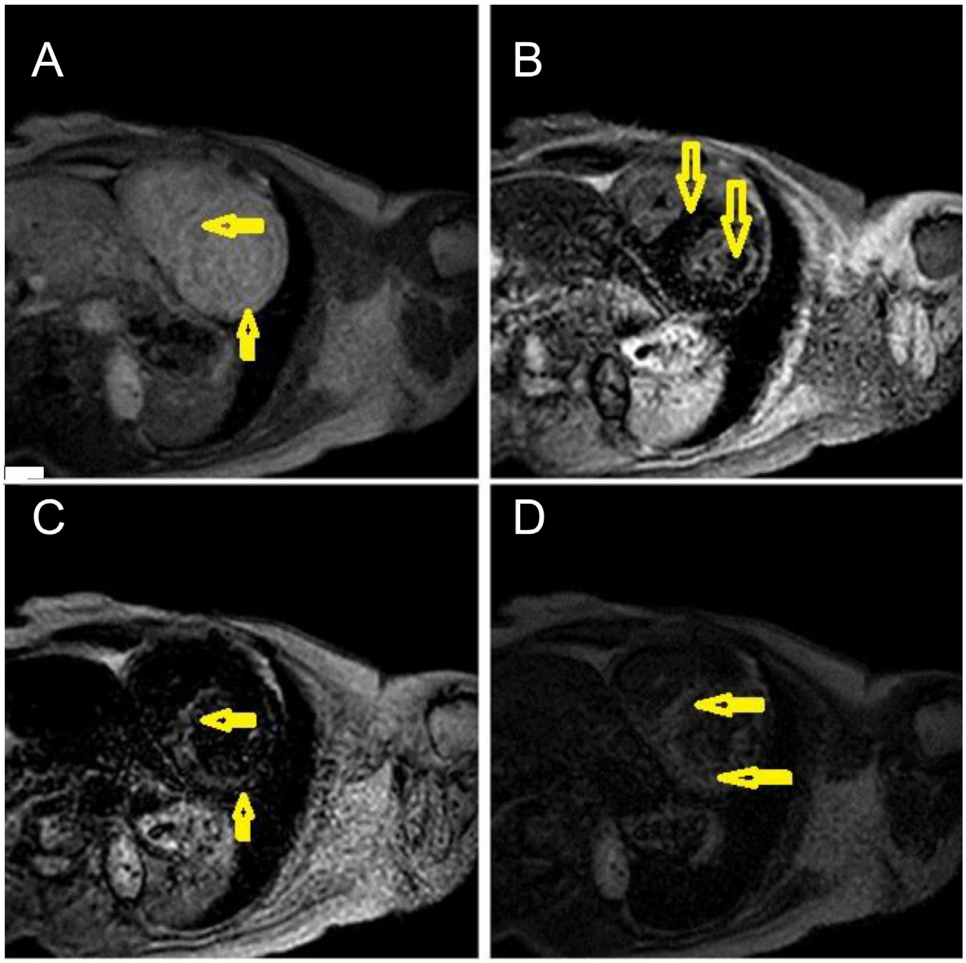

Fig. 5 – Short axis time to invert T1 scout image of left ventricle showing increasing inversion time from (A) to (D) abnormal nulling pattern initially blood pool, myocardium and spleen all bright (A), myocardium null before blood (B) blood pool nulls next (C) and finally spleen (D).

initial assessment of CM to facilitate early diagnosis and risk stratification, which can impact targeted therapy and survival rates [9].

On postcontrast images invert T1 scout images, in normal nulling pattern (NNP), the blood pool nulls before the myocardium, and the myocardium nulls in coincidence with the spleen. The nulling of myocardium at T1 lower than that of the blood pool or nulling not coincide with the spleen is considered as abnormal nulling pattern (ANP) [10]. In our patient, the nulling of the myocardium in relation to the blood pool and the spleen was assessed and the short axis time to invert T1 scout image of left ventricle showed increasing inversion time with the myocardium initially nulling before the blood pool nulls, and finally the spleen, which is a typical ANP. The ANP has sensitivity of 46.6 %, however, it has 100% specificity for cardiac amyloidosis when present [11]. Another previous study demonstrated that the ANP of the myocardium, blood pool, and spleen on T1 scout sequence of CMR has 100% sensitivity for amyloid detection, and recommends evaluating the temporal pattern of nulling as an adjunct in the diagnosis of cardiac amyloidosis [12].

Conclusion

Cardiac amyloidosis is a rare disease that can present a diagnostic challenge. Echocardiography serves as an excellent imaging modality for screening and guiding further testing. CMR is the standard method for assessing asymmetric myocardial thickening and diagnosing cardiac amyloidosis. It utilizes LGE MR images to reveal patterns of enhancement, and postcontrast images invert T1 scout images to detect the abnormal nulling patterns. In this report, we review typical findings that should raise suspicion for diagnosis and guide further evaluation.

Author contributions

EA: provided CMR examination, collected and interpreted data. SAA: wrote the manuscript. AMH: interpreted and revised data. MAA& AMO: edited language, and revised the

manuscript. All authors revised the final version and equally responsible for the contents of the manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used [ChatGPT] in order to [improve language and readability]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Ethical approval

This study was done in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Before data collection, written informed consent was acquired after the study was well explained. The laboratory procedure was done with the essence of beneficence and data were kept confidential.

Patient consent

Before data collection, written informed consent was acquired after the study was well explained.

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