Cardiac amyloidosis, report of 2 cases with strain echocardiography and cardiovascular magnetic resonance

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ABSTRACT

We present 2 cases of cardiac amyloidosis cases with strain echocardiography and cmr. The first case was a 68-year-old female with previous refractory heart failure due to chronic coronary syndrome. The second case was a 51-year-old female patient who was admitted in our center with marked dyspnea for 2 months. Both cases were performed with electrocardiogram, chest X ray, transthoracic echocardiography and cardiovascular magnetic resonance. Both patients was performed serum immunology test which showed elevated free light chains (FLC) kappa and κ/λ ratio. These patients were suggested the diagnosis of AL cardiac amyloidosis and treated with chemotherapy.

Keywords: cardiac amyloidosis, light chain amyloidosis, transthyretin amyloidosis, strain echocardiography.

1. INTRODUCTION

Cardiac amyloidosis is an infiltrative cardiomyopathy caused by aggregates of abnormal fibrillar proteins in the heart tissue (Guan et al., 2012; Martinez-Naharro et al., 2018). The type of amyloidosis defined by the precursor protein (Hirschfield and Hawkins, 2003). The four most common precursor proteins associated with cardiac amyloidosis are AL (light chain amyloidosis), wild-type transthyretin, mutant TTR and localized atrial amyloid deposits (Ruberg and Berk, 2012). Amyloid deposits lead to abnormal function of the heart, cardiac amyloidosis is the most typical restrictive cardiomyopathy with nonspecific clinical findings (Guan et al., 2012). We report two cases of cardiac amyloidosis that were diagnosed by cardiac ultrasound, especially strain echocardiography, cardiac MRI associated with genetic testing and serum protein electrophoresis.
2. CASE PRESENTATION

Case 1
A 61 yr. old man patient presented in our MEDIC center by dyspnea that was notified since 2 years ago, previous diagnosis including hypertrophic cardiomyopathy and atrial fibrillation had been noted. Physical examination detected a 3rd gallop sound, jugular vein distension, hepatomegaly, lower extremity edema with oliguria. The treatment of congestive heart failure did not improve his symptoms, the clinical feature suggested the refractory end stage HF. Blood test showed the high concentration of plasma NT-Pro BNP=2263pg/ml. A sinus rhythm with VPB, poor R and dominant S wave in precordial leads were revealed on his ECG (Figure 1). Chest X ray showed a cardiomegaly with enlarged LV arch and incresead PVM (Figure 2).

Routine 2D Echocardiography demonstrated bialtrial enlargement, LV thickening with severely reduced EF (IVSd= 17mm, PWd=15mm, LVDd=42mm, EF=22%), especially granular texture of LV myocardium (sparkling appearance) visualized. Strain Echocardiography demonstrated GLS-endo-peak-A4C, A2C, A3C and GLS-endo-peak-Avg that were severely reduced, consecutively equal to -3.2%, -5.2%, -8.3%, -5.6% (Figure 3 - 6). CMR showed the characteristic pattern of transmural late gadolinium enhancement (Focal patchy LGE). The myocardium reached the null point before the blood pool. Myocardial nulling technique was used to make the distinction between cardiac amyloidosis and other cardiomyopathies, notably hypertrophic cardiomyopathy. Genetic testing confirmed the diagnosis of ATTR cardiac amyloidosis: ATTR variant ( NM_000371.3 ), c.424G>A ( p.Val142Ile) mutation.

![Figure 1](image1.png) ECG showed QS waves in DIII, DIII, aVF and V1 V2 V3 like the old infarction and VPB.

![Figure 2](image2.png) Chest X ray showed a cardiomegaly with enlarged LV arch and increased PVM.
**Figure 3** A: Parasternal LAX view demonstrated the thickening of LV walls (IVSd=17mm, PWd=15mm) with marked reduce of LV systolic function (EF=21.6%). B: LAX view especially revealed the myocardial infiltration which was seen as the typical ground glass appearance.

**Figure 4** A: Parasternal SAX view showed the same image of ground glass appearance and the small pericardial effusion. B: Apical 4 C views showed biatrial enlargement, thickening of IAS and LVH with myocardial infiltration.

**Figure 5** A: Pulse Doppler of mitral flow visualized a marked increased E/A ratio=2.4. B: TDI visualized the restrictive type or diastolic dysfunction of grade III: E/e' med=24.
Figure 6 2D Speckle Tracking showed marked reduce of GLS in the most basal and medial segments, notified preserved strains in apical and anterior segments.

Cardiac MRI especially using the following sequences (Figure 7). Cine MRI (Steady state free precession, Double IR FSE T1 (Double inversion recovery fast Spin Echo T1 or Dark blood), Triple IR FSE T2 (Triple inversion recovery fast Spin Echo T2 or Dark blood and Fat-sat), 2D MDE 2RR= LGE- MRI.

Figure 7 A: Cine MRI sequence showed biatrial enlargement, LV hypertrophy and small pericardial effusion. B: Dark bood and Fat-sat or Triple IR FSE T2 demonstrated the myocardial hyper-signal, especially subendocardial area. C: Myocardial nulling technique used to null the signal from normal myocardium during delayed- enhanced imaging; the LGE was diffuse in myocarde.

Case 2
A 51 yr. old man patient, presented in our MEDIC center by marked dyspnea since 2 months. Physical examination detected 3rd gallop sound, jugular vein distension, hepatomegaly, lower extremity edema. The treatment of congestive heart failure by diuretics improved his symptoms a little; the clinical feature suggested the stage C of heart failure. A sinus rhythm with low electrical voltage and QS waves were seen in precordial leads V1V2V3 on his ECG (Figure 8). Chest X ray showed a cardiomegaly with enlarged LV arch (Figure 9). Transthoracic Echocardiography demonstrated biatrial enlargement, LVH with marked reduce of systolic function (IVSd= 20mm, PWd=17mm, LVDd=47mm, EF=33%), sparkling appearance was visualized on 2D and 3D imaging’s (Figure 10 - 14).

Cardiac MRI using Triple IR FSE revealed the myocardium which reached the null point (282msec) before the blood pool (389msec).Late gadolinium enhancement of myocardium diffusely presented at 10 minutes. Serum immunology test demonstrated increased FLC kappa (412 mg/L) and κ/λ ratio (16.35), suggested the diagnosis of AL cardiac amyloidosis. Patient was informed about the chemotherapy.
Figure 8 ECG showed low voltage of peripheral leads and QS in V1 V2 V3 like the anteroseptal old infarction (pseudo-infarct).

Figure 9 Chest X ray visualized a cardiomegaly with enlarged LV arch and increased PVM.

Figure 10 A: Parasternal LAX view demonstrated the thickening of LV walls (IVSd=20mm, PWd=17mm) with marked reduce of LV. B: Apical 4 C view showed LV hypertrophy with the sparkling sign of myocardium, biatrial enlargement and thickening of IAS.
**Figure 11** A: Parasternal LAX view visualized sparkling sign and a small pericardial effusion. B: The same image with Tissue Doppler Imaging. Sparkling sign still was visible.

**Figure 12** A: Restrictive filling of diastolic dysfunction, E/A ratio=2.7. B: Restrictive physiology: decreased septal velocity, elevated E/e’med=28.

**Figure 13** A: CW of TR flow demonstrated a slight systolic pulmonary artery pressure, peak gradient = 26mmHg. B: TM mode of TV annulus showed normal systolic function of RV, TAPSE-16.5mm.
Figure 14  A: Live 3D of parasternal LAX showed LV hypertrophy and irregular echodensity of myocardium. B: Live 3D of apical 4C view provided LV hypertrophy and irregular density of IVS.

3. DISCUSSION

Clinical findings: cardiac amyloidosis, a disease resulting from the aggregates of amyloid proteins in the myocardial extracellular matrix that leads to restrictive cardiomyopathy (Siddiqi and Ruberg, 2018; Taiwo et al., 2019). Cardiac amyloidosis is difficult to diagnose because of nonspecific clinical manifestations, the most patient are admitted by severe congestive HF and arrhythmias (Kozak et al., 2021; Morais et al., 2014). Two patients in our study were presented by marked dyspnea and edema which were manifestations of advanced heart failure. Two patients were male and one patient of 61y.o had mutant ATTR, other of 51y.o referred to AL like previous descriptions. Low ECG voltage in limb leads and prefrontal QS waves like old anterior infarct were seen clearly at our patients. Low voltage complexes are seen in 49% of AL cases, 27% of vATTR, pseudo anterior infarct pattern is seen in 39% of AL cases, 23% of vATTR. Cardiomegaly with enlarged LV arch was detected in 2 patients due to important LVH.

Echocardiography is the most widely used and valuable noninvasive diagnostic method which provides significant cardiac abnormalities, several of which are highly suggestive of the disease before starting CMR (Esmaeilzadeh et al., 2013; Refoyo et al., 2020). Regarding morphology of cardiac amyloid, our patients had typical characteristic of echocardiographic findings: important concentric wall thickening of LV with irregular echodensity of myocardium, (IVSd+ PWd)/2 > 12mm (16mm for 1st patient and 18.5mm for 2nd patient), further more increased size of LA and RA, IAS thickening, small pericardial effusion. Especially echocardiographic imaging demonstrated a typical granular sparkling echo-reflectance, the entire of myocardium notably IVS were more dense than normal (Miyagawa et al., 2020; Suresh et al., 2014). This granular texture of myocardium is an important echocardiographic clue to make the diagnosis of cardiac amyloidosis, especially in presence of LV thickening but ECG low voltage, restrictive filling diastolic dysfunction, severely reduced longitudinal strain, “Cherry on the top” on speckle tracking or relative apical sparing in echocardiography (Yamamoto and Yokochi, 2019; Yilmaz et al., 2021). This apical sparing on speckle tracking results from the conserved longitudinal strain of the apical area and used to make the distinction between cardiac amyloidosis and other cardiomyopathies with LVH, notably hypertrophic cardiomyopathy (Stelmach-Goldys et al., 2022; Stern and Kittleson, 2021; Ti and Zhang, 2020).

Cardiac magnetic resonance imaging (Cardiac MRI or CMR) is an advanced noninvasive technology for assessment the structure and the function of the heart. CMR in our center was performed on GE Explorer 1.5Tesla machine, QVI 4.2 software with IV Gadovist. Cine MRI is the most valuable imaging method to determine the thickening of walls, the sizes of cavities as well as detect the pericardial effusion (Stassen et al., 2021). The steady state free precession sequences as Steady state free precession, Double inversion recovery Fast Spin Echo T1 used to study the morphology, cardiac function, wall motion (Rigopoulos et al., 2019; Simoes et al., 2021). We applied the Triple FSE T1 sequence to null signal from normal myocardium during delayed enhancement imaging. Triple IR FSE: the myocardium reached the null point (282 msec) before the blood pool (389msec) on the second patient. Like Strain Echocardiography, this important CMR finding makes the distinction between cardiac amyloidosis and other cardiomyopathies with LVH, notably hypertrophic cardiomyopathy.

Late gadolinium enhancement is the hallmark feature for diagnosis of cardiac amyloidosis, LGE has prognostic value also, transmural extension of amyloid infiltration like 2 patients in our study associated with important cardiac involvement as marked reduced EF, severe heart failure (Oubari et al., 2021; Pankuweit and Dorr, 2022). In order to our experience, routine echocardiography is first clue suggesting the diagnosis of cardiac amyloidosis in presence of LV wall thickening associated with ECG low voltage or pseudo-infarct waves, especially “granular sparkling appearance” a characteristic finding of amyloid.
infiltration and restrictive diastolic pattern are seen on echographic imaging (Law et al., 2021; Legrand et al., 2022). Further more severely reduced longitudinal strain with apical sparing on speckle tracing echocardiography makes the typical echographic impairment of cardiac amyloidosis like my first patient (Garcia-Pavia et al., 2021b; Kitaoka et al., 2020).

CMR using null points technique during delayed enhancement imaging is the hallmark feature for diagnosis of cardiac amyloidosis, makes a difference between cardiac amyloidosis and other cardiomyopathies with LVH, mainly hypertrophic cardiomyopathy (Garcia-Pavia et al., 2021a). CMR associated with genitic testing in first patient and serum electrophoresis in second one confirmed the diagnosis of ATTR and AL in our study (Chen and Dilsizian, 2020; Fazlinezhad and Naqvi, 2020). Advances in cardiac imaging like speckle tracking echo and CMR with multiple sequences have facilitated the diagnosis of disease, led to a non-invasive diagnostic approach, thus limited the need for endomyocardial biopsy (Alexander et al., 2019; Bonderman et al., 2020; Boyle et al., 2021).

4. CONCLUSION
Cardiac amyloidosis is an infiltrative cardiomyopathy caused by deposits of abnormal amyloid fibrils which are defined by precursor proteins. The most common types of amyloidosis are AL, then Wild type ATTR, and Mutant ATTR. Patients usually presented very late in hospital by symptoms of congestive heart failure due to restrictive pattern diastolic dysfunction.

Consent for Publication
Written informed consent for publication of the clinical details and clinical images was obtained from the patients.

Author’s contribution
Duc Minh Nguyen and Tuan Vu Nguyen contributed equally to this article.

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Conflicts of interest
The authors declare that there are no conflicts of interests.

Data and materials availability
All data associated with this study are present in the paper.

REFERENCES AND NOTES

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