Wild type transthyretin cardiac amyloidosis in a young individual
A case report

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Abstract

Rationale:Senile systemic amyloidosis, a disease of elderly is caused by amyloid deposition of wild-type transthyretin. The symptoms often overlap with other heart diseases. Hence it is either misdiagnosed or considered as a normal aging process in majority of cases.

Patient concerns:We present a young patient of wild-type transthyretin amyloidosis, contradicting its only senile presence. The 34-year-old man presented with dyspnoea on exertion. He was suffering from hypertension for consecutive 3 years.

Diagnosis:Echocardiography demonstrated left ventricular hypertrophy with reduced global longitudinal strain and apical sparing. Congo red staining and immuno-histochemical staining of the abdominal fat biopsy confirmed transthyretin amyloid deposition. Genetic analysis revealed absence of any mutant variant/s of transthyretin gene, confirming wild-type transthyretin amyloidosis.

Intervention:A combination of amiodipine 5 mg, telmisartan 40 mg, and chlorthalidone 12.5 mg once daily was given to control the blood pressure of the patient.

Outcome:Blood pressure was controlled but he continued to have exertional dyspnoea. The patient expired in December 2019.

Lessons:A systematic diagnosis for wild type transthyretin amyloid cardiomyopathy (ATTR-CM) shall be considered in young cardiac patients suffering from cardiac distress with unknown etiology.

Abbreviations:κ = kappa, λ = lambda, AL = immunoglobulin light chain, ATTR-CM = transthyretin amyloid cardiomyopathy, ATTRwt = wildtype transthyretin, EFSR = ejection fraction to strain ratio, LFT = liver function test, LGE = late gadolinium enhancement, LVH = left ventricular hypertrophy, mg = milligram, MRI = magnetic resonance imaging, PCR = polymerase chain reaction.

Keywords:cardiac amyloidosis, case report, transthyretin, wildtype, young

1. Introduction

Cardiac amyloidosis is characterized by the extracellular deposition of some amyloid precursor proteins in the myocardium of heart. The systemic form of cardiac amyloidosis is mainly driven by either the misfolded monoclonal immunoglobulin light chains (kappa and lambda) or transthyretin.[1] The symptoms of cardiac amyloidosis often overlap with symptoms of other cardiovascular diseases mostly hypertrophic cardiomyopathy. Hence, in majority of cases, it is often overlooked and remains undiagnosed. In the recent years, incidence of transthyretin related amyloidosis has increased across the world.[2] However, there are no published reports on transthyretin-related cardiac amyloidosis from India. In this direction, researchers in collaboration with the clinicians have started sensitizing for the need of systematic diagnosis of amyloidosis in India.[3]

With this effort, for the first time, we are reporting a case of senile systemic amyloidosis in a young individual from India.

2. Case report

A 34-year-old male patient from North India presented with exertional dyspnea stage II (New York Heart Association) without any chest pain or pedal swelling. He was hypertensive for 3 years, not controlled with amiodipine 5 mg once daily. There
was no family history of inflammatory disease, heart failure or premature cardiac death. His pulse rate was 84 beats per minute with all peripheral pulses palpable. Jugular venous pressure was not elevated. There was no lymphadenopathy and organomegaly, suggested by abdominal ultrasonography. Routine hematological and biochemical parameters including renal and liver function test (LFT) profile were within the normal range. The electrocardiogram of the patient suggested left ventricular hypertrophy (LVH) with strain pattern and sinus rhythm (Fig. 1A). Trans-thoracic echocardiography showed evidence of asymmetric LVH (LVH) with inter-ventricular septal diameter of 2.4 cm (yellow arrow) in diastole (Fig. 1C) along with speckled pattern in the myocardium (D, E) without any evidence of left ventricular outflow tract gradient or systolic anterior motion of anterior mitral valve leaflet (F, G). Tissue Doppler study revealed grade 2 left ventricular diastolic dysfunction (H, I). Strain echocardiography using speckled tracking revealed marked diminution of global longitudinal strain with apical sparing (J). LVH= left ventricular hypertrophy.

Figure 1. Surface electrocardiogram of the patient showing evidence of left ventricular hypertrophy (red box and yellow box) with strain pattern (arrow) (A). Trans-thoracic echocardiography showing evidence of asymmetric LVH (B) with inter-ventricular septal diameter of 2.4 cm (yellow arrow) in diastole (C) along with speckled pattern in the myocardium (D, E) without any evidence of left ventricular outflow tract gradient or systolic anterior motion of anterior mitral valve leaflet (F, G). Tissue Doppler study revealed grade 2 left ventricular diastolic dysfunction (H, I). Strain echocardiography using speckled tracking revealed marked diminution of global longitudinal strain with apical sparing (J). LVH=left ventricular hypertrophy.
showed a reduced global longitudinal strain of −8.7% with apical sparing (Fig. 1J), classically known as “cherry on top” pattern, suggesting cardiac amyloidosis. Ejection fraction to strain ratio (EFSR) was calculated as 5.51. Left atrial volume index was 40 mL/m² with an evidence of mild mitral regurgitation and trivial tricuspid regurgitation, suggestive of diastolic dysfunction. Coronary angiogram showed normal epicardial coronary arteries. Nerve conduction velocity study revealed no evidence of carpal tunnel syndrome. Cardiac magnetic resonance imaging (MRI) was performed but it showed no late gadolinium enhancement (LGE). Immuno

Figure 2. Microscopy images of Congo red stained abdominal fat biopsy tissue specimen under polarized light (A) and unpolarized light (B) confirming amyloidosis. Light microscopy image of anti-TTR antibody stained fat tissue specimen showing positive reaction in amyloid enriched areas (C). Scale bar: 200 μm.

3. Discussion

Senile systemic amyloidosis, caused by wildtype transthyretin (ATTRwt) is considered as the disease of aged individuals with more severity in octogenarians.[4] However, the patient being young makes this case more fascinating than the earlier published reports where the youngest case reported was 47 years old.[5] Reduced global longitudinal strain (−15.1%) with apical sparing pattern and an EFSR value of >4.1 are reported echocardiogram features for cardiac amyloidosis. These features differentiate it from other causes of LVH by 72%, 82%, and 92% specificity respectively.[6,7] Echocardiogram of our patient also reflected these same features. The presence of LVH in echocardiogram and pseudo-infarct pattern along with sinus rhythm in electrocardiogram are common features found in transthyretin amyloid cardiomyopathy (ATTR-CM) patients.[8,9] Our patient also showed evidences of asymmetric LVH in the echocardiogram and pseudo-infarct pattern along with sinus rhythm in the electrocardiogram, suggesting ATTR-CM. Moreover, presence of “cherry on top” pattern in the bull eye plot in the 2 dimensional speckle tracking echocardiographic findings of our patient also provided significant cues for ATTR amyloidosis despite of the absence of low voltage in the electrocardiogram.[10] This was consistent with the echocardiographic findings of our patient too. LGE pattern might be absent in some ATTRwt cases and was also true for our case.[11] The presence of monoclonal gammopathy along with renal impairment and macroglossia is highly implicated in case of immunoglobulin light chain (AL) amyloidosis.[4] However, our patient did not show such features. Besides, abnormal serum FLC k/λ ratio with an elevated FLC level in the absence of a monoclonal protein is often found in ATTRwt patients.[12,13] Our patient also showed an elevated kappa light chains and k/λ ratio without M spike, suggesting involvement of wildtype transthyretin. Endomyocardial biopsy is the gold standard for confirming the presence of amyloid deposits in heart by classical Congo red dye staining. But, it involves certain risks as well as expertise in handling.[14] However, literature suggests that abdominal fat biopsy can also type ATTR amyloidosis with significant confidence.[15,16] In case of our patient, histopathological examination of the abdominal fat biopsy specimen revealed extensive amyloid deposits derived from transthyretin. It was confirmed as wild type by genetic analysis.
4. Conclusion
To the best of our knowledge, this is the first report of transthyretin-related amyloidosis from India. So far, this is also the youngest case of wild-type transthyretin reported in the world. This study will stimulate the cardiologists to carry a systematic approach to diagnose wild-type transthyretin-related amyloidosis not only in elderly but in young patients as well.

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References
[1] Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. Circulation 2020;142:e7–22.
[2] Ruberg FL, Grogan M, Hanna M, et al. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol 2019;73:2872–91.
[3] Thakur AK, Ghosh S, Gahane AY. Amyloidosis: a strong need for clinical diagnosis in India. Amyloid 2019;26:175–6.
[4] Rubin J, Maurer MS. Cardiac amyloidosis: overlooked, underappreciated, and treatable. Annu Rev Med 2020;71:203–19.
[5] Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol 2016;68:1014–20.
[6] Pagourelas ES, Mirea O, Duchenne J, et al. Echo parameters for differential diagnosis in cardiac amyloidosis: a head-to-head comparison of deformation and nondeformation parameters. Circ Cardiovasc Imaging 2017;10:e005388.
[7] Phelan D, Collier P, Thavendiranathan P, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart 2012;98:1442–8.
[8] González-López E, Gagliardi C, Dominguez F, et al. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. Eur Heart J 2017;38:1895–904.
[9] Dany T, Costes B, Hagège AA, et al. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. Eur Heart J 2016;37:1826–34.
[10] Dany T, Maurer MS, Rapezzi C, et al. Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy. Open Heart 2016;3:e000289.
[11] Baroni M, Nava S, Quattrrocchi G, et al. Role of cardiovascular magnetic resonance in suspected cardiac amyloidosis: late gadolinium enhancement pattern as mortality predictor. Neth Heart J 2018;26:34–40.
[12] Geller HI, Singh A, Mirto TM, et al. Prevalence of monoclonal gammopathy in wild-type transthyretin amyloidosis. Mayo Clin Proc 2017;92:1800–5.
[13] Sidiqi MH, Dasari S, McPhail ED, et al. Monoclonal gammopathy plus positive amyloid biopsy does not always equal AL amyloidosis. Am J Hematol 2019;94:E141–3.
[14] Leone O, Veinot JP, Angeli A, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 2012;21:245–74.
[15] Fine NM, Arruda-Olson AM, Dispenzieri A, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. Am J Cardiol 2014;113:1723–7.
[16] Ikeda S-i, Sekijima Y, Tojo K, et al. Diagnostic value of abdominal wall fat pad biopsy in senile systemic amyloidosis. Amyloid 2011;18:211–5.