Transthyretin cardiac amyloidosis

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Abstract

Transthyretin amyloid cardiomyopathy (ATTR-CM) may be an under recognized cause of heart failure (HF). TTR amyloidosis can be inherited, caused by variants in the TTR gene (ATTRv) or by deposition of wild-type TTR protein (ATTRwt), leading to high mortality if untreated. We report the case of a patient with hereditary TTR amyloidosis and mixed phenotype (both cardiac and neurological involvement). We highlight the importance of multimodal imaging in the evaluation of these patients, as early diagnosis and treatment might lead to better outcome.

Keywords: TTR amyloidosis, transthyretin, multimodality imaging

Introduction

TTR amyloidosis is a rare disease, which necessitates an extensive workup upon presentation. Current data in literature show that in the absence of specific treatment, the median survival is of 2.5 years for ATTRv and 3.6 years for ATTRwt [1].

We report the case of a patient diagnosed with TTR cardiac amyloidosis with mixed phenotype, who presented a good clinical outcome under treatment with Tafamidis.

Case report

A 69-year-old hypertensive male patient was referred to the cardiology department for dyspnea, limited exercise tolerance and numbness at the level of the lower limbs for the past 3 months. The past history was unremarkable.

On admission the patient was hemodinamicaly stable. There were no significant findings on clinical examination. Although an electro-cardiogram (ECG) performed 3 years had with no significant changes, the current ECG showed a major left bundle branch block.

Transthoracic echocardiography (TTE) revealed thickened left ventricular (LV) walls (the interventricular septum was of 23 mm and the inferolateral wall of 15 mm) in the presence of normal LV cavity, preserved systolic function (the left ventricular ejection fraction was of 65%) and grade II diastolic dysfunction (E/e'=20). These characteristics raised the suspicion of an infiltrative cardiomyopathy (Figure 1a). We subsequently performed a speckle-tracking analysis, which revealed apical sparing, as shown in figure 1b. Therefore, the suspicion of cardiac amyloidosis was raised.

Notable biological tests were a NT-proBNP of 546 pg/mL, hs-TnI of 0.23 ng/mL. The patient had normal creatinine and did not present proteinuria.

Cardiac magnetic resonance imaging (CMR) confirmed the echocardiographic findings and showed a shorter inversion time of the myocardium compared to intracavitary blood. There was late gadolinium enhancement (LGE) with subendocardial distribution, but there was transmural distribution at the level of the lateral LV wall (Figure 2). The clinical picture was suggestive of cardiac amyloidosis.

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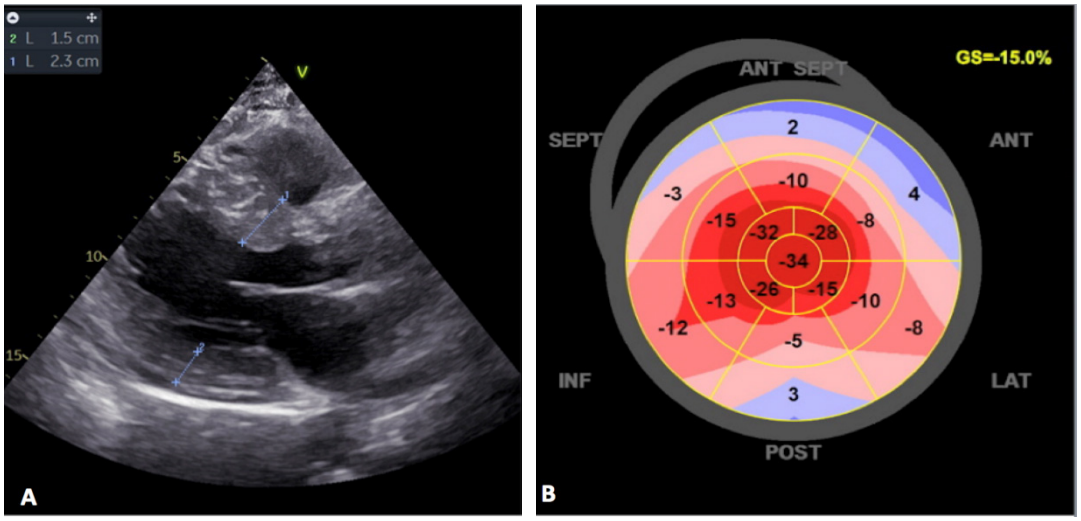

Figure 1. Transthoracic echocardiography showing increased left ventricular wall thickness (**A**) and the typical apical sparing (**B**).

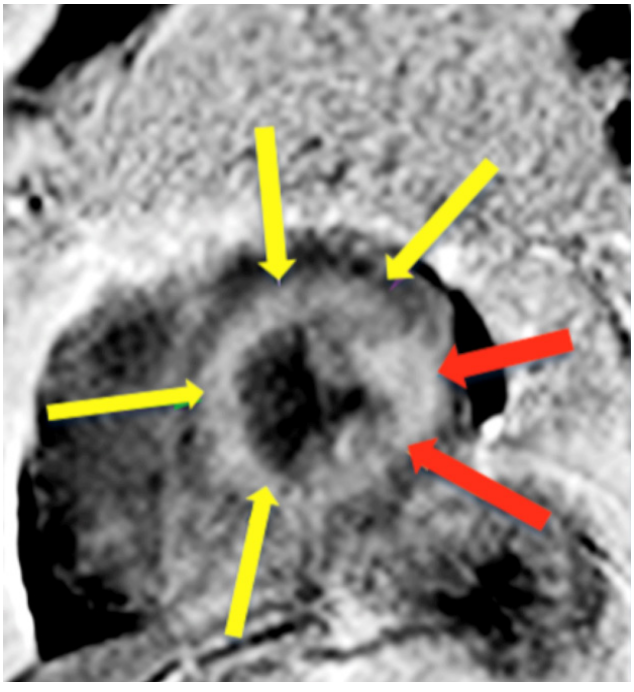

Figure 2. Cardiac magnetic resonance imaging showing LGE with subendocardial (yellow arrows) and transmural distribution (red arrows).

Subsequent bone scintigraphy with 99mTc-HDP showed significant cardiac uptake, with a Perugini score of 3 (Figure 3). These imaging findings, in association with serum and urine immunofixation and serum free light chain assay, which were all negative, confirmed the diagnosis of ATTR-CM. Moreover, the patient was positive for a mutation in the TTR gene (E109V), confirming ATTRv. Screening of the patient's two children was negative for this TTR mutation.

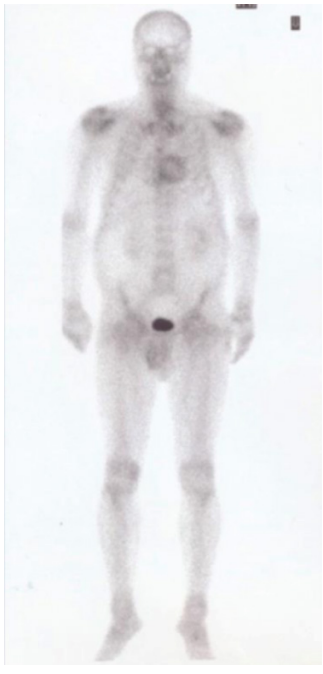

Figure 3. Bone scintigraphy showing cardiac uptake (corresponding Perugini score of 3). Further neurology investigations diagnosed peripheral autonomic neuropathy.

The patient started therapy with Tafamidis (20 mg OD). On 1-year follow-up, the patient's effort capacity and neurological condition improved. Follow-up CMR showed a similar LGE distribution as on initial evaluation (Figure 4).

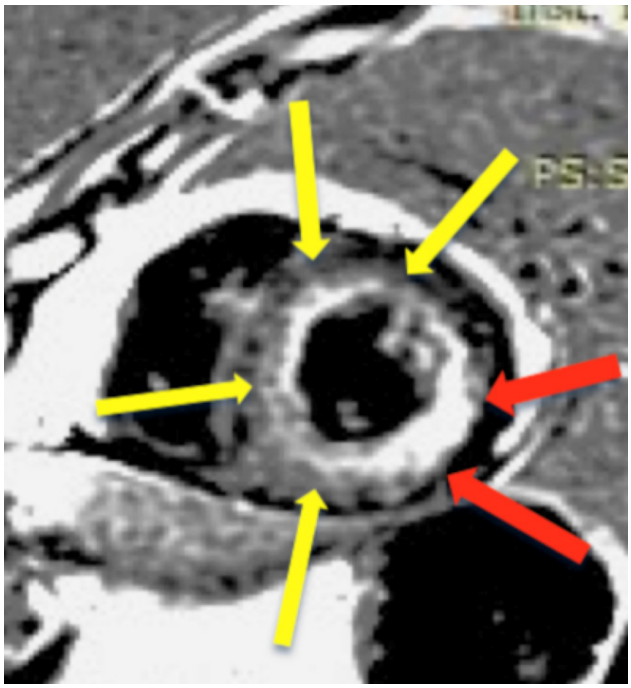

Figure 4. Follow-up cardiac magnetic resonance imaging showing LGE with subendocardial (yellow arrows) and transmural distribution (red arrows). The LGE distribution at 1-year was similar to the initial investigation.

Discussion

ATTR-CM is associated with significant mortality. Regarding the symptomatology, dyspnea, fatigue and edema are most frequently encountered, but they are usually misdiagnosed as non-amyloid HF [1,2].

During the last 3 years, there has been advancement regarding both the diagnosis and treatment of TTR-CM, including findings regarding imaging techniques that allow a precise diagnosis in the absence of endomyocardial biopsies [1-3] and discovery of novel disease-modifying therapies [4-6].

Multimodality imaging (TTE and CMR) is used to raise the suspicion of cardiac wall infiltration. Echocardiography might reveal increased LV wall thickness and small LV cavity in the presence of a preserved LV ejection fraction. These findings are usually associated with pericardial effusion and impaired global longitudinal strain, with the characteristic apical sparing [1,7]. All of these features were also found in our patient. CMR might also be an indicator of the infiltrative process by showing elevated native T1, higher extracellular volume fraction and late gadolinium enhancement, with typical subendocardial or transmural distribution [1,8]. Our patient demonstrated transmural LGE at the level of the lateral LV wall.

Even though echocardiography and CMR indicate cardiac infiltration, the use of 99mTc bone-avid compounds actually allows the noninvasive diagnosis of ATTR-CM [9]. However the basis for binding to amyloid remains unknown. Although bone scintigraphy is the cornerstone in the diagnosis of ATTR-CM, up to 40% of patients with AL cardiac amyloidosis also demonstrate positive scans. Thus, immunofixation electrophoresis and light chain concentration are mandatory for the exclusion of a protein dyscrasia [1]. In our case, the patient presented significant cardiac uptake on scintigraphy, in the absence of protein dyscrasia, confirming the diagnosis of TTR cardiac amyloidosis.

Besides cardiac investigations, such patients also require neurologic assessment in order to diagnose autonomic neuropathy, which is frequently associated. In these patients, although the quality of life is primarily affected by the neuropathy, the prognosis and survival time are actually determined by the cardiomyopathy [10].

After identification of ATTR-CM, genetic sequencing of the TTR gene is necessary to differentiate between ATTRv and ATTRwt, since the genetic variant also requires screening of the family members [11]. In our case, all other family members were negative for the mutation.

Because therapy for ATTR-CM is most effective when administered before significant cardiac dysfunction, early diagnosis of affected patients with noninvasive testing is important. Tafamidis is a TTR stabilizer, which was approved in May 2019. In a recent study (ATTR-ACT, Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy), Tafamidis was associated with a significantly lower mortality and cardiovascular-related hospitalization after 30 months in both ATTRwt and ATTRv cardiomyopathy [4]. At 1-year follow-up, both cardiac and neurological symptoms improved and there was no LGE progression on CMR in our patient, confirming the better outcome after early diagnosis and specific therapy in TTR amyloidosis.

Conclusion

We recommend the consideration of TTR amyloidosis as a differential diagnosis in patients with heart failure and neuropathy.

References

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