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CASE REPORT
Heart failure

A case report of transthyretin amyloidosis following cardiac transplantation: thick ventricles that look alike

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Background Transthyretin (ATTR) amyloidosis is more prevalent than initially thought. As much as 13% of patients hospitalized with heart failure with preserved ejection fraction may have ATTR-cardiomyopathy (CM). Conversely, heart transplant patients may manifest left ventricular hypertrophy or diastolic dysfunction, especially late after transplantation.

Case summary We present a case of a 82-year-old male heart transplant patient, 31 years following orthotopic heart transplantation. While he was satisfied with his exercise capacity as an octogenarian, several years before, he required pacemaker implantation due to third-degree atrioventricular block, had bilateral carpal tunnel syndrome treated with carpal tunnel release surgery, and experienced idiopathic sudden deafness. Based on increasing left ventricular wall thickness during routine follow-up, a diagnosis of ATTR amyloidosis was suspected. Ultimately, the diagnosis was confirmed non-invasively with a specific scintigraphic exam, while an additional physico-chemical stain on an endomyocardial biopsy taken several years before provided pathological proof. We initiated tafamidis, yet stopped this treatment after 1 month because of gastrointestinal intolerance. Ultimately, our patient died 2 years later due to heart failure.

Discussion Our case shows the long delay between the onset of ATTR deposition, the presence of clinical signs, and the final diagnosis. Echocardiographic findings suggestive for ATTR-CM include left ventricular hypertrophy and diastolic dysfunction, which are both common in heart transplant patients. Yet, ATTR-CM should be considered in the differential diagnosis, especially late after transplantation, in this closely monitored population.

Keywords Cardiac transplantation • Amyloidosis • Heart failure • Cardiac imaging • Biomarkers • Case report

ESC curriculum 6.3 Heart failure with preserved ejection fraction • 2.1 Imaging modalities • 2.3 Cardiac magnetic resonance • 2.5 Nuclear techniques • 6.5 Cardiomyopathy

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Learning points

- Cardiac transthyretin (ATTR) amyloidosis should be considered as a cause of heart failure with preserved ejection fraction in long time survivors after cardiac transplantation.
- Elements in the (non-)cardiac medical history might suggest the diagnosis in this closely monitored patient population.
- Echocardiographic findings suggestive for ATTR-cardiomyopathy (CM) include left ventricular hypertrophy and diastolic dysfunction, which are both common in heart transplant patients.
- A definite diagnosis can be made non-invasively with a specific scintigraphic exam or invasively with an endomyocardial biopsy to which a Congo Red staining is applied.
- Available drugs that prevent ATTR synthesis in the liver or additional deposition of ATTR amyloid in target organs can be used as these drugs are immunologically inert and do not seem to augment the risk of allograft rejection.

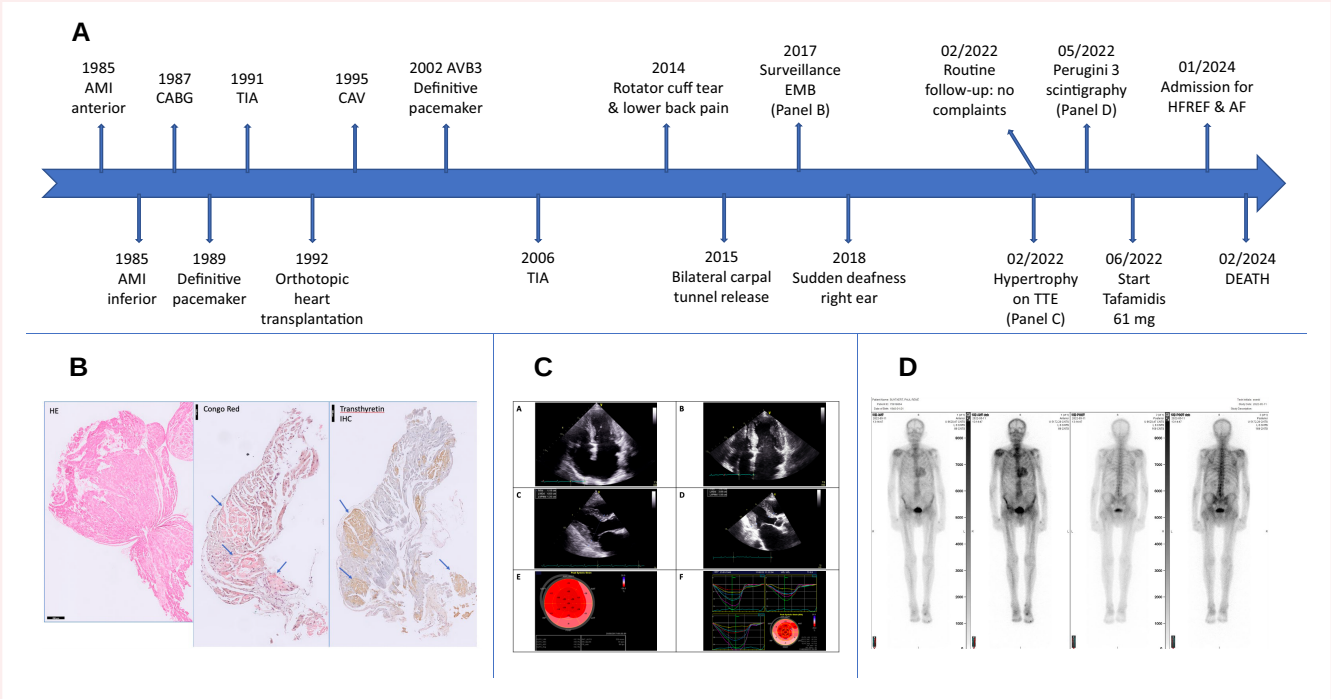
Introduction

Recent studies have shown that transthyretin (ATTR) amyloidosis is more prevalent than previously thought and often not suspected as a cause of common cardiac conditions such as heart failure with preserved ejection fraction (HFpEF), aortic stenosis, and atrial fibrillation.[1,2] Despite increased awareness among healthcare providers and broader use of cardiac scintigraphy, the true prevalence of ATTR amyloidosis remains unknown.[1] Autopsy studies have shown that the incidence increases with age,[3] and among older patients hospitalized with HFpEF, 13% were found to have ATTR-cardiomyopathy (CM) on bone scintigraphy.[4] Until now, there have been no reports of ATTR-CM in orthotopic heart transplant patients.

Summary figure

Case presentation

We describe a case of an 82-year-old male who underwent an orthotopic heart transplantation (biatrial or Shumway surgical technique) in 1992 because of end-stage ischaemic heart failure. The donor was a 28-year-old male. When he was evaluated in February 2022, he generally felt well and denied dyspnoea and other complaints suggestive of cardiac disease. His general physical and cardiovascular exam was unremarkable. His past medical history was significant for cardiac allograft vasculopathy (1995), a third-degree AV block requiring a dual-chamber pacemaker [magnetic resonance imaging (MRI) incompatible] (2002), transient ischaemic attacks (2006), bilateral carpal tunnel syndrome treated with carpal tunnel release surgery (2015), and a history of sudden deafness (2018). The indication for pacemaker implantation was attributed at the time to the biatrial surgical technique used (12.1% vs. 5.4% with bicaval technique),[5] although this could also be an early



Timeline (*A*). Results of endomyocardial biopsy from 2017 with, from left to right, haematoxylin eosin stain, Congo Red stain, and transthyretin immunohistochemical stain (*B*). Echocardiographic exam in February 2022 (*C*). Perugini 3 bone scintigraphy results in May 2022 (*D*). AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAV, cardiac allograft vasculopathy; EMB, endomyocardial biopsy; HFREF, heart failure with reduced ejection fraction; TIA, transient ischaemic attack; TTE, transthoracic echocardiography.

manifestation of ATTR fibril deposition. Routine follow-up beyond the first year following transplantation consisted of 3-monthly outpatient visits, each time with transthoracic echocardiography. At our centre, endomyocardial biopsies (EMBs) are routinely taken in the first post-operative year, according to the International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients, and when clinically indicated thereafter.[6] Cardiac amyloidosis was suggested by increased left ventricular wall thickness on routine echocardiography and by apical sparing on strain rate imaging. A bone scintigraphy showing ATTR amyloid deposition (Perugini grade 3) confirmed the diagnosis. To further substantiate the diagnosis, a Congo Red stain was performed on a surveillance EMB taken in 2017 (25 years following cardiac transplantation); this physicochemical stain showed amyloid deposition. The ensuing immunohistochemical stains were positive for ATTR. At the time the EMB was taken, the patient had no complaints and echocardiography showed no signs of diastolic dysfunction (*Summary figure* and Supplementary material online). Treatment with tafamidis 61 mg was initiated, yet interrupted after 1 month due to gastrointestinal intolerance. Our patient died at the age of 84 during an episode of acute heart failure, 2 years after the diagnosis of ATTR-CM (February 2024).

Discussion

To the best of our knowledge, this is the first description of the development of ATTR amyloidosis in a patient after heart transplantation.

As mentioned above, ATTR amyloidosis is more prevalent than previously thought and causes common cardiac conditions such as HFpEF, aortic stenosis, and atrial fibrillation.[1,2] Tafamidis stabilizes ATTR and thus halts further progression of ATTR amyloid deposition. For this reason, greater benefit is achieved when administered early in the disease course.[7] However, this case demonstrates that cardiac deposition is already present several years before clinical signs become apparent. In our case, there was a delay of at least 5 years between first positive EMB and the clinical diagnosis of ATTR-CM. Importantly, left ventricular wall thickness was not increased at the time an EMB was taken in 2017, yet increased markedly thereafter, providing a hint to the diagnosis. Typical echocardiographic findings in ATTR-CM are a diffuse and symmetrical increase in wall thickness, diastolic dysfunction with impaired relaxation in early stages progressing to a restrictive filling pattern in advanced amyloidosis. The systolic function remains preserved until later stages, and global longitudinal strain typically shows an impaired basal/mid segmental strain with preserved apical longitudinal strain with a typical pattern on the so called bull's eye representation of regional longitudinal strain values.[8,9] However, diastolic dysfunction is also prevalent in the transplanted population. Post-cardiac transplantation diastolic dysfunction can be divided into early and late, with early diastolic dysfunction being related to the status of the donor heart, the acute effects of transplantation, and cardiovascular abnormalities of the recipient. Early diastolic dysfunction often returns to normal.[6,10,11] In contrast, Valantine and colleagues showed that late diastolic dysfunction occurs in a subgroup of transplant recipients in which a restrictive filling pattern correlated with a marked increase in heart failure symptoms and a history of acute rejections episodes.[12]

With this case as an example and the knowledge that ATTR amyloidosis is common in patients with HFpEF, while diastolic dysfunction correlates with heart failure symptoms in long-term transplanted patients, it could be interesting to routinely include appropriate studies to detect ATTR-CM in this closely monitored population.

Our case demonstrates the delay between ATTR deposition and clinical signs becoming apparent. In our opinion, a low threshold for further investigations should be kept when echocardiographic signs are suggestive for amyloidosis. Cardiac MRI may be a useful first additional imaging tool in this specific population. Specific MRI findings for ATTR-CM include left ventricular hypertrophy, diffuse subendocardial or transmural late gadolinium enhancement (LGE), and elevated extracellular volume (ECV) on T1 mapping sequences.[13,14] However, cardiac MRI may frequently be impossible, as was the case in our patient, due to MRI incompatibility of previously implanted (cardiac) electronic devices.

Lastly, we hypothesize that donor-derived amyloidogenic ATTR fibrils ('self') are sufficient to develop into amyloid irrespective of the recipient interstitial antigenic make-up ('non-self').

Conclusion

We report a case of ATTR amyloidosis developing during long-term follow-up after cardiac transplantation. Although left ventricular wall thickening and diastolic dysfunction is common following heart transplantation, clinicians should also consider ATTR amyloidosis of the cardiac allograft in the differential diagnosis. Further studies are needed to determine ATTR-CM epidemiology following transplantation and the efficacy of its treatment in this specific patient population.

Lead author biography

Charlotte Lauwers is a cardiologist in training at the University Hospitals of Leuven (Leuven, Belgium), with special interest in imaging and heart failure.

Supplementary material

Supplementary material online is available at *European Heart Journal – Case Reports* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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