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(CASE REPORT)

Transthyretin cardiac amyloidosis: Case report with literature review

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Abstract

Transthyretin cardiac amyloidosis includes both senile or wild-type amyloidosis (ATTRwt) and hereditary amyloidosis (ATTRv), which are related to a mutation in the transthyretin gene. This pathology is characterized by the extracellular accumulation of insoluble fibrillary proteins that progressively impair myocardial function. The prognosis depends on the severity of the cardiac involvement. Cardiac manifestations are nonspecific and include symptoms of heart failure and/or conduction and rhythm disturbances (atrial flutter and fibrillation). The diagnosis of cardiac amyloidosis has greatly improved over the past ten years and relies on multimodal imaging, primarily echocardiography, cardiac MRI, and bone scintigraphy. We report the case of a 71-year-old patient presenting with global heart failure in the context of transthyretin cardiac amyloidosis. This case provides an opportunity to review the literature on cardiac involvement related to this condition, as well as the differential diagnoses of restrictive cardiomyopathies.

Keywords: Restrictive cardiomyopathy; Left ventricular hypertrophy; Heart failure; Transthoracic echocardiography; Cardiac MRI

1. Introduction

Cardiac amyloidosis is a rare but serious condition, often underdiagnosed, resulting from abnormal extracellular deposits of amyloid fibrillar proteins within the myocardial tissue. These deposits progressively alter the structure and function of the heart, leading to restrictive cardiomyopathy, heart failure, and arrhythmias. Long considered an incurable disease, cardiac amyloidosis has recently garnered renewed interest due to advances in diagnostic and therapeutic approaches, particularly in transthyretin (ATTR) and light chain (AL) forms. This article aims to provide an overview of the pathophysiological mechanisms, diagnostic methods, and therapeutic options for this underrecognized but potentially treatable condition.

2. Clinical Case

We report the case of a 71-year-old patient with cardiovascular risk factors, including recently diagnosed well-controlled hypertension under ARBs, type 2 diabetes for 2 years managed with oral hypoglycemic agents, and a history of bilateral carpal tunnel syndrome surgery 15 years ago. The patient was admitted for the management of progressively worsening dyspnea associated with increased volume in both lower limbs.

On clinical examination, the patient weighed 88 kg with a height of 1.74 m, resulting in a BMI of 29 kg/m^2. The pulse was regular at 92 bpm, and blood pressure was 140/78 mmHg. Cardiac auscultation revealed clear heart sounds with a regular rhythm and no murmurs. Edema was present in both lower limbs up to the knees. Pulmonary auscultation revealed fine crackles at the lung bases.

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The ECG showed a regular sinus rhythm with a heart rate of 90 bpm, normal heart axis, PR interval of 200 ms, and evidence of left ventricular hypertrophy with secondary repolarization abnormalities.

Chest X-ray showed cardiomegaly with right heart enlargement and signs of pulmonary hypertension. Biologically, renal function was normal (creatinine clearance of 70 ml/min), with elevated NT-ProBNP (1600 ng/L), and normal troponin levels.

Transthoracic echocardiography revealed a non-dilated left ventricle with hypertrophied walls and a granular appearance of the myocardium, moderate systolic dysfunction with an ejection fraction (EF) of 44% in systolic blood pressure (SBP), and a severely altered global longitudinal strain (GLS) at –9.2%, with a "bull's-eye" pattern (Figure 2). Right ventricular free wall hypertrophy was noted at 7 mm, with good right ventricular systolic function. The atria were dilated with elevated filling pressures, a high probability of pulmonary hypertension, and a pericardial effusion of 8 mm posteriorly and 7 mm laterally to the right ventricle. The inferior vena cava (IVC) was dilated and poorly compliant. No valvular abnormalities were detected.

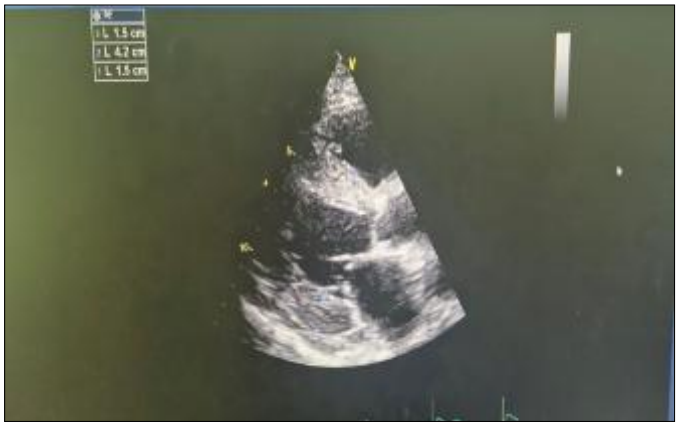

Figure 1 Concentric left ventricular hypertrophy

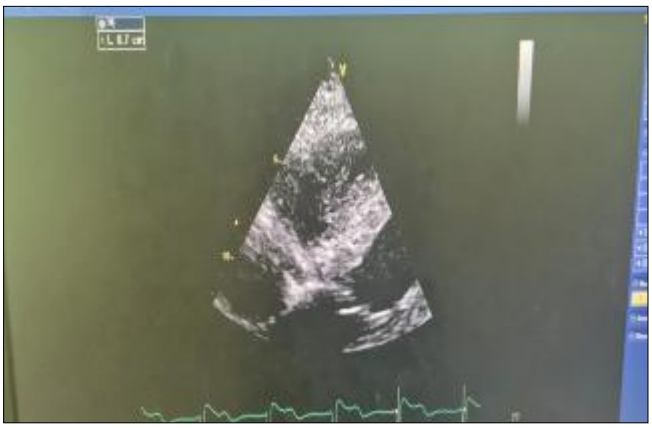

Figure 2 Right ventricular hypertrophy

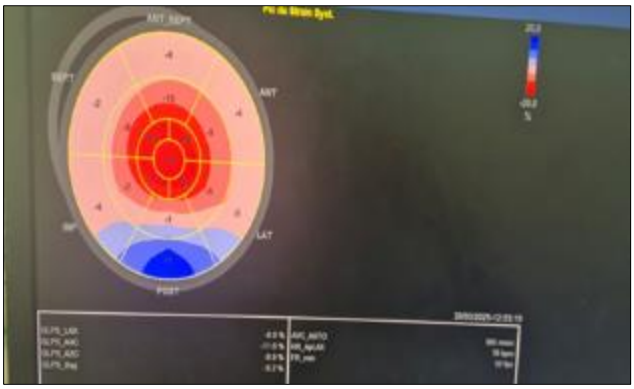

Figure 3 Longitudinal strain abnormalities with a bull's-eye pattern

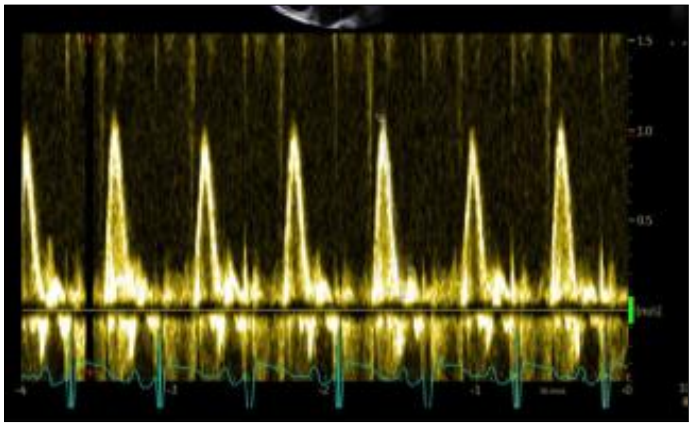

Figure 4 Restrictive mitral flow

- **Cardiac MRI** shows a non-dilated left ventricle with diffuse wall hypertrophy, with a maximum thickness of 17 mm, and moderately impaired systolic function with an ejection fraction (EF) of 41%. There is hypertrophy of the right ventricular free wall with preserved systolic function (right ventricular EF of 45%). Late-phase imaging reveals diffuse late enhancement with a "rail track" appearance of the left ventricle, atria, and interatrial septum. The atria are dilated**.** There is a circumferential pericardial effusion with a maximum thickness of 17 mm posteriorly.

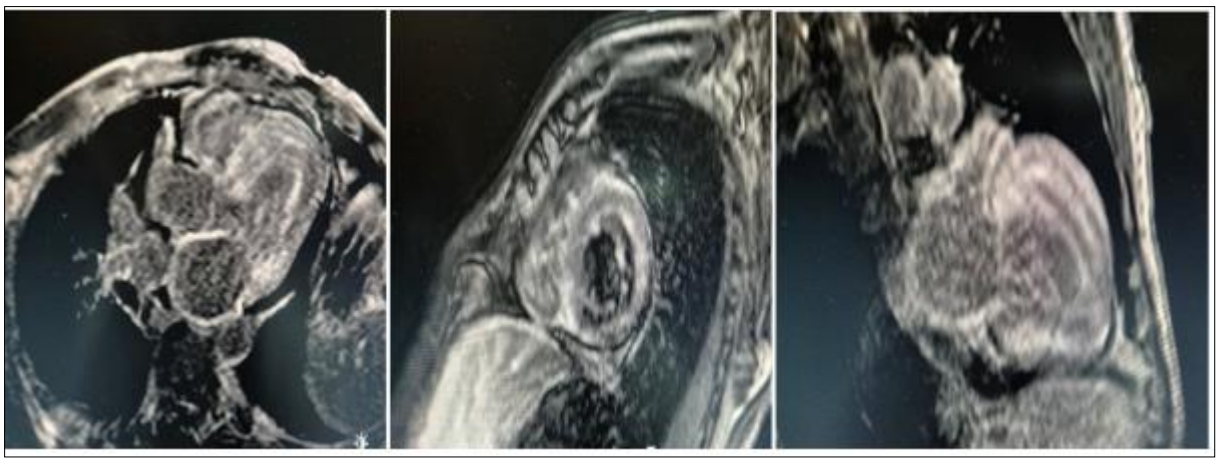

Figure 5 Late sequence in short axis, four-chamber, and two-chamber views showing diffuse left ventricular hypertrophy with diffuse subendocardial late enhancement and a "rail track" appearance

The patient underwent blood and urine tests (including Bence Jones proteinuria search), which included serum protein electrophoresis, immunofixation, and measurement of free light chains of Ig, coupled with a whole-body scintigraphy using DPD (99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid). The blood and urine tests ruled out a monoclonal peak and an imbalance of Ig light chains, thus not supporting a light chain (AL) amyloidosis. Whole-body DPD scintigraphy showed hyperfixation in the cardiac area on the whole-body views, classified as stage 3 of Perugini, which was further confirmed on tomographic slices.

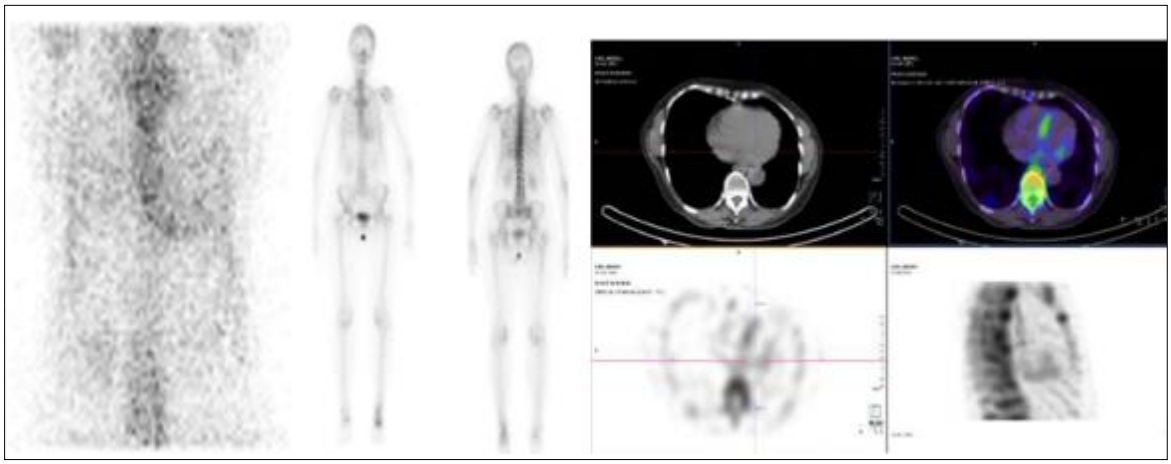

Figure 6 Whole-body DPD scintigraphy in late-phase images showing cardiac hyperfixation without extinction of the bone frame (stage 2 of Perugini). Cardiac tomographic slices combined with whole-body DPD scintigraphy confirm myocardial hyperfixation (and not intracardiac blood pool as sometimes observed in cases of slowed blood flow)

Molecular genetic analyses for TTR were performed, and no known pathogenic variant was found in this gene, so the "wild-type" TTR amyloidosis diagnosis was retained. A Holter ECG was requested as an additional test to monitor high-grade conduction disturbances requiring pacemaker implantation, as well as atrial or ventricular arrhythmias. The patient was started on diuretic treatment with a good response, followed by the initiation of specific therapy after requesting management approval.

3. Discussion

Amyloidoses are systemic diseases characterized by the extracellular accumulation of insoluble fibrillary proteins that deposit and infiltrate tissues, preventing their normal functioning. (1) Amyloidoses are classified based on the biochemical nature of the amyloid protein involved in the formation of deposits. About twenty proteins can form amyloid fibrils (transthyretin, immunoglobulin light chains, fibrinogen, apo A1, etc.) [1]. The most common form of cardiac amyloidosis is transthyretin amyloidosis (ATTR) [2], which is classified into two types:

- Wild-type ATTR, formerly known as senile systemic amyloidosis, which accounts for 13% of heart failure with preserved left ventricular ejection fraction (LVEF) and 16% of aortic stenosis in men undergoing transcatheter aortic valve implantation (TAVI) [2].
- Hereditary ATTR: the familial form where the transthyretin (TTR) gene is mutated (ATTRv, "v" for variant) [2]. The inheritance is autosomal dominant. Over 120 pathogenic mutations of the gene encoding TTR have been identified, and their prevalence varies by country and with improvements in cardiological diagnosis [3]. Tissue involvement varies depending on the mutation and results in different phenotypes: cardiac, neurological, or mixed. In a multicenter study, 6% of hypertrophic cardiomyopathies were associated with a mutation of the TTR gene [4, 5].

Cardiac manifestations are nonspecific and include symptoms of heart failure and/or conduction and rhythm disturbances (atrial flutter and atrial fibrillation).

Q waves are frequently observed on the electrocardiogram and are related to the extent of amyloid infiltration. Extracardiac manifestations are diverse, and most occur several years before cardiac manifestations [6]. They could aid in the earlier detection of ATTR [6]. These manifestations vary depending on the type of amyloidosis: carpal tunnel syndrome, deafness [7], rupture of the long biceps tendon, lumbar spinal stenosis, and more rarely in ATTRv, as in AL: periorbital ecchymosis and macroglossia. Neurological involvement predominates in ATTRv, affecting the autonomic

nervous system and peripheral nerves, with involvement of length-dependent fibers. Autonomic nervous system involvement can be prominent in ATTRv, affecting all autonomic functions, leading to severe orthostatic hypotension, gastroparesis responsible for intractable vomiting causing hypokalemia, and disturbances in genitourinary functions. These manifestations significantly impair the quality of life of patients [8]. Natriuretic peptides are frequently elevated and reflect increased intraventricular pressure due to myocardial stiffness (infiltrative process). Myocyte injury, resulting from myocardial infiltration, is indicated by chronic elevation of troponin I and T (in the absence of coronary artery disease). The elevation of these markers has allowed the establishment of severity scores in amyloidosis and the impact of specific treatments [9;10], [11], [12]. Echocardiography and magnetic resonance imaging (MRI) are complementary in the diagnostic approach but do not distinguish between the different forms of amyloidosis. On echocardiography, left ventricular hypertrophy is often significant in ATTR (≥15 mm) and is most often concentric. Contractility impairment is measured by 2D longitudinal strain. The "bull's-eye" appearance with apical sparing is highly suggestive of amyloidosis [13]. Diastolic dysfunction is common, with a restrictive profile in the later stages. Pericardial effusion may be associated. The presence of the triad—right and left ventricular hypertrophy and pericardial effusion—is very suggestive of amyloidosis but indicates an advanced stage. Cardiac MRI details the morphological abnormalities described above. Amyloid deposits are visualized by late gadolinium enhancement. This enhancement is due to the stagnation of gadolinium and is also observed in myocardial fibrosis. The enhancement can be subendocardial or diffuse and may be present in all myocardial walls, strongly favoring an infiltrative process. Difficulty or inability to properly adjust the inversion time (TI) to differentiate the myocardium from the blood pool due to gadolinium retention is also observed [11].

Myocardial scintigraphy with diphosphonates is the key exam for diagnosing cardiac involvement in ATTR [14]. Diphosphonate tracers (DPD, HMDP) used in bone scintigraphy label amyloid deposits.Cardiac.

The cause of cardiac fixation is not known. Intense myocardial fixation on scintigraphy is highly suggestive of ATTR (hereditary or wild-type), especially if there is no associated gammopathy. This is why bone tracer scintigraphy and gammopathy screening have become essential examinations in the etiological workup of hypertrophic cardiomyopathies [14], necessary to differentiate ATTR amyloidosis with gammopathy. Transthyretin gene sequencing is performed for the diagnosis of hereditary transthyretin amyloidosis [10].

The therapeutic management of heart failure in amyloidosis aims to limit water and sodium retention by adjusting volume status [10]. Beta-blockers are particularly harmful in severe forms due to their negative inotropic, dromotropic, and chronotropic effects: in cardiac amyloidosis, cardiac output primarily depends on heart rate. Anticoagulation is often necessary due to the high risk of thromboembolic events in patients with cardiac amyloidosis. Atrial arrhythmias are common in cardiac amyloidosis, and controlling the heart rate can be challenging. Pacemaker implantation may be useful in some symptomatic patients with marked chronotropic incompetence. Since the pathological process is progressive and dynamic, it is essential to constantly reevaluate the risk of conduction disturbances (third-degree AV block, bundle branch block) by monitoring PR and QRS intervals and their prolongation. Resynchronization therapy can be considered in cases with preserved LVEF, particularly if there is a risk, or especially if there is a higher risk.

The combination of aortic stenosis and cardiac amyloidosis confers a worse prognosis, especially if the stenosis has low flow and low gradient; however, the performance of a transcatheter aortic valve implantation (TAVI) improves the prognosis in patients with both conditions [15]. The treatment for ATTR cardiac amyloidosis is VYNDAQEL® (tafamidis). Tafamidis is a specific stabilizer of transthyretin (TTR) [16], [17], [18]. It binds to TTR at its thyroid hormone-binding sites, thereby inhibiting the dissociation of the tetramer. Treatment should be initiated by a cardiologist specializing in the care of patients with wild-type ATTR. For patients with hereditary ATTR (ATTRv) with a predominant cardiac form, tafamidis is recommended, as it has shown an improvement in survival in the ATTRACT study. Cardiac fixation decreases with tafamidis [19].

4. Conclusion

The diagnosis of cardiac amyloidosis has greatly improved over the past decade. Recognizing this condition is crucial because the cardiological management is specific, and only targeted treatments can slow down or halt the infiltrative process. The development of targeted treatments, increased awareness among healthcare professionals, and access to non-invasive diagnostic tools play an essential role in this progress. However, many challenges remain, particularly in terms of systematic screening, access to innovative treatments, and comprehensive patient management. A multidisciplinary and individualized approach remains essential to optimize survival chances and quality of life for patients with cardiac amyloidosis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] S. Oghina, M.A. Delbarre, E. Poullot, K. Belhadj, P. Fanen, T. Damy Cardiac amyloidosis: State of art in 2022Rev Med Interne, 43 (2022), pp. 537-544

[2] J.C. Eicher, S. Audia, T. Damy Transthyretin cardiac amyloidosis Rev Med Interne, 41 (2020), pp. 673-683

[3] T. Damy, A.V. Kristen, O.B. Suhr, M.S. Maurer, V. Planté-Bordeneuve, C.R. Yu, et al.Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOSEur Heart J, 43 (2019), pp. 391-400

[4] T. Damy, B. Costes, A.A. Hagège, E. Donal, J.C. Eicher, M. Slama, et al.Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thicknessEur Heart J, 37 (2016), pp. 1826-1834

[5] T. Damy, M.S. Maurer, C. Rapezzi, V. Planté-Bordeneuve, O.N. Karayal, R. Mundayat, et al. Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy Open Heart, 3 (2016), p. e000289

[6] M. Kharoubi, M. Bézard, A. Galat, F. Le Bras, E. Poullot, V. Molinier-Frenkel, et al.History of extracardiac/cardiac events in cardiac amyloidosis: prevalence and time from initial onset to diagnosisESC Heart Fail, 8 (2021), pp. 5501-5512

[7] E. Béquignon, A. Guellich, S. Bartier, M. Raynal, V. Prulière-Escabasse, F. Canouï-Poitrine, et al.How your ears can tell what is hidden in your heart: wild-type transthyretin amyloidosis as potential cause of sensorineural hearing loss in elderly-AmyloDEAFNESS pilot study Amyloid, 24 (2017), pp. 96-100

[8] T. Damy, D. Adams, F. Bridoux, G. Grateau, V. Planté-Bordeneuve, Y. Ghiron, et al.Amyloidosis from the patient perspective: the French daily impact of amyloidosis study Amyloid, 29 (2022), pp. 165-174

[9] M. Kharoubi, D. Bodez, M. Bézard, A. Zaroui, A. Galat, S. Guendouz, et al. Describing mode of death in three major cardiac amyloidosis subtypes to improve management and survival Amyloid, 29 (2022), pp. 79-91

[10] M.S. Maurer, S. Bokhari, T. Damy, S. Dorbala, B.M. Drachman, M. Fontana, et al.Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis Circ Heart Fail, 12 (2019), p. e006075

[11] L. Bonnefous, M. Kharoubi, M. Bézard, S. Oghina, F. Le Bras, E. Poullot, et al. Assessing cardiac amyloidosis subtypes by unsupervised phenotype clustering analysis J Am Coll Cardiol, 78 (2021), pp. 2177-2192

[12] J.D. Gillmore, T. Damy, M. Fontana, M. Hutchinson, H.J. Lachmann, A. Martinez-Naharro, et al.A new staging system for cardiac transthyretin amyloidosis Eur Heart J, 39 (2018), pp. 2799-2806

[13] J. Ternacle, D. Bodez, A. Guellich, E. Audureau, S. Rappeneau, P. Lim, et al.Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis JACC Cardiovasc Imaging, 9 (2016), pp. 126-138

[14] A. Galat, J. Rosso, A. Guellich, A. Van Der Gucht, S. Rappeneau, D. Bodez, et al. Usefulness of (99 m)Tc-HMDP scintigraphy for the etiologic diagnosis and prognosis of cardiac amyloidosis Amyloid, 22 (2015), pp. 210-220

[15] J. Ternacle, L. Krapf, D. Mohty, J. Magne, A. Nguyen, A. Galat, et al. Aortic stenosis and cardiac amyloidosis: JACC review topic of the week J Am Coll Cardiol, 74 (2019), pp. 2638-2651

[16] M.S. Maurer, J.H. Schwartz, B. Gundapaneni, P.M. Elliott, G. Merlini, M. Waddington-Cruz, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy N Engl J Med, 379 (2018), pp. 1007-1016

[17] S. Oghina, C. Josse, M. Bézard, M. Kharoubi, M.A. Delbarre, D. Eyharts, et al.Prognostic value of N-terminal pro-brain natriuretic peptide and high-sensitivity troponin T levels in the natural history of transthyretin amyloid cardiomyopathy and their evolution after tafamidis treatment J Clin Med, 10 (2021), p. 4868

[18] S. Odouard, M. Abulizi, M. Kharoubi, S. Oghina, S. Guendouz, A. Zaroui, et al. Tafamidis decreases cardiac uptake of 99mTc-HMDP in transthyretin cardiac amyloidosis JACC Cardiovasc Imaging, 15 (2022), pp. 2149-2151

[19] P. Garcia-Pavia, F. Bengel, D. Brito, T. Damy, F. Duca, S. Dorbala, et al. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy Eur J Heart Fail, 23 (2021), pp. 895-905