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Research paper

Challenges in the approach to a patient with aortic stenosis and cardiac amyloidosis with ATTR mutation associated with negative scintigraphy - A case report

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ABSTRACT

Introduction: Cardiac amyloidosis (CA) poses significant diagnostic and therapeutic challenges. In this case report, we detail a patient with CA due to a rare transthyretin (CA-TTR) mutation, manifesting with negative myocardial scintigraphy and requiring genetic testing for diagnosis. The patient also had severe aortic stenosis (AS), necessitating discussion with a heart team to determine the optimal treatment strategy.

Case report: A 70-year-old male with a family history of sudden death was previously diagnosed with third-degree atrioventricular block and treated with a pacemaker. He presented with worsening exertional dyspnoea, and examination revealed a third heart sound, a systolic murmur indicative of AS and bilateral muscular atrophy in the thenar region. Transthoracic echocardiography indicated severe AS and moderate left ventricular dysfunction, with images suggesting infiltrative disease. Pyrophosphate scintigraphy revealed no abnormal cardiac tracer uptake. Cardiac magnetic resonance imaging (MRI) revealed extensive, heterogeneous, subendocardial late gadolinium enhancement in both the atria and ventricles, which was consistent with CA. Genetic testing identified the Phe84Leu mutation in the TTR gene. Following heart team discussions, the patient underwent successful transcatheter aortic valve implantation (TAVI) and remained asymptomatic in follow-up, being monitored at an outpatient clinic specializing in CA and using tafamidis.

Discussion: CA-TTR can be an autosomal dominant disease with variable penetrance involving abnormal amyloid protein deposition in tissues and can often be diagnosed noninvasively via myocardial scintigraphy. However, some TTR mutations do not affect scintigraphy results, necessitating genetic testing when clinical suspicion is high, potentially avoiding endomyocardial biopsy. Moreover, AS occurs in up to 16 % of TTR amyloidosis patients, with the conditions mutually exacerbating each other. Recent consensus suggests that TAVI reduces mortality in patients with severe AS and amyloidosis.

Conclusions: Various diagnostic algorithms emphasize the use of myocardial scintigraphy for suspected CA-TTR. Genetic testing is crucial when scintigraphy results are negative, but clinical suspicion remains high, potentially circumventing invasive procedures. Compared with medical management alone, TAVI has been shown to improve quality of life and survival in patients with concurrent severe AS and CA.

1. Case report

A 70-year-old self-identified black male patient presented to the hospital with a complaint of dyspnoea that had started a year prior and progressed on exertion. At the time of admission, he was classified as New York Heart Association (NYHA) Functional Class III. He denied

having chest pain, syncope, or any other symptoms during this period or at any previous time.

Regarding his personal history, the patient had been diagnosed with systemic arterial hypertension for 30 years, was a current smoker with an estimated smoking history of 50 pack-years and had a dual-chamber pacemaker implanted at the same hospital 3 years prior due to

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atrioventricular block. He also had benign prostatic hyperplasia and was classified as having stage IIIb chronic kidney disease (CKD) according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification.

Regarding family history, the patient disclosed that his mother died suddenly at the age of 35 and that his sister had a history of heart failure with multiple hospitalizations. He was unaware of any history of disease on his father's side.

On physical examination at the emergency room, the patient was awake, alert, oriented, and haemodynamically stable, with a blood pressure of 128/84 mmHg and a heart rate of 72 beats. He maintained good oxygen saturation (99 %) and had a respiratory rate of 18 breaths per minute. The cardiovascular examination revealed diminished and delayed carotid arterial pulses, jugular venous distention with hepatojugular reflux, and a palpable apical impulse at the sixth intercostal space along the left midclavicular line. Auscultation revealed a regular three-beat cardiac rhythm with the presence of a fourth heart sound, as well as a systolic diamond-shaped murmur heard at the aortic area, graded as 2+/6+, radiating to the sternum. Pulmonary auscultation revealed crackling crepitations in the lower thirds of both lung fields with no breath sounds in the right lung base. The patient also had abdominal distention suggestive of mild-to-moderate ascites, symmetrical and painless +3/4+ oedema in the lower limbs with positive pitting, as well as muscle atrophy in both hands and bilateral median nerve percussion tenderness. Symmetrical bilateral reduced sensitivity was observed in the lower limbs, with no other neurological abnormalities on examination.

A diagnosis of decompensated heart failure syndrome presented with systemic congestion without signs of poor perfusion associated with aortic stenosis (AS) and a haemodynamically stable clinical presentation, as well as peripheral neuropathy, and the patient was admitted to the hospital ward. Upon admission, clinical stabilization measures, including intravenous diuretic therapy, were implemented. Initially, beta-blockers and vasodilators were avoided because of the presence of AS on physical examination. The following laboratory results were obtained: haematocrit, 41.8 %; WBC, 7000/ μ L; platelets, 164,000/ μ L; glucose, 71 mg/dL; HbA1c, 6 %; BUN, 55.7 mg/dL; creatinine, 1.76 mg/dL; globulin, 3.5 g/dL; triglycerides, 59 mg/dL; LDL-C, 121 mg/dL; NT-

proBNP, 7014 pg/mL; troponin, 0.12 ng/mL; 24-hour proteinuria, 83.5 mg/dL; and 24-hour urinary volume, 1610 mL.

The admission electrocardiogram revealed sinus rhythm with ventricular pacing by the pacemaker.

A chest X-ray (Fig. 1) revealed cardiomegaly, right-sided pleural effusion, and the presence of the pacemaker device.

Transthoracic echocardiogram (TTE) (Figs. 2 and 3) revealed enlargement of all four chambers, primarily the atria, with biventricular hypertrophy and both systolic and diastolic dysfunction, with a global longitudinal strain of -3.9 %. Furthermore, there were alterations indicative of infiltrative disease, including increased thickness and echogenicity, known as myocardial sparkling, in the left ventricular (LV) walls, particularly in the interventricular septum. No preserved apical contraction was observed during the apical sparing assessment. Additionally, the aortic valve exhibited significant calcification, with immobility of two of its leaflets, resulting in a maximum LV/aortic gradient of 18 mmHg and a mean gradient of 11 mmHg. The stroke volume was 30 mL/ m^2 , and the estimated valve area was 0.9 cm^2 , leading to a diagnosis of severe AS with the classic low-flow low-gradient pattern and mild aortic regurgitation.

Following the completion of this examination, in addition to confirming severe AS, the presence of infiltrative disease was suggested, which prompted further comprehensive investigations. A serological assay for free light chain (kappa and lambda) and serum protein electrophoresis along with serum and urine immunofixation were performed, yielding negative results. Additional evaluations were subsequently conducted, starting with pyrophosphate scintigraphy (Figs. 4 and 5), which did not reveal abnormal tracer uptake in the cardiac region. This was followed by cardiac magnetic resonance imaging (MRI) (Figs. 6 and 7), which depicted extensive and heterogeneous late gadolinium enhancement. This enhancement pattern was notably more intense in the subendocardium and affected both ventricles diffusely. Moreover, it extended to encompass the walls of both atria. This specific enhancement pattern is consistent with nonischemic myocardial injury of an infiltrative nature, suggestive of amyloidosis.

Given the strong clinical suspicion of cardiac amyloidosis (CA) despite negative scintigraphy and immunoglobulin test results and

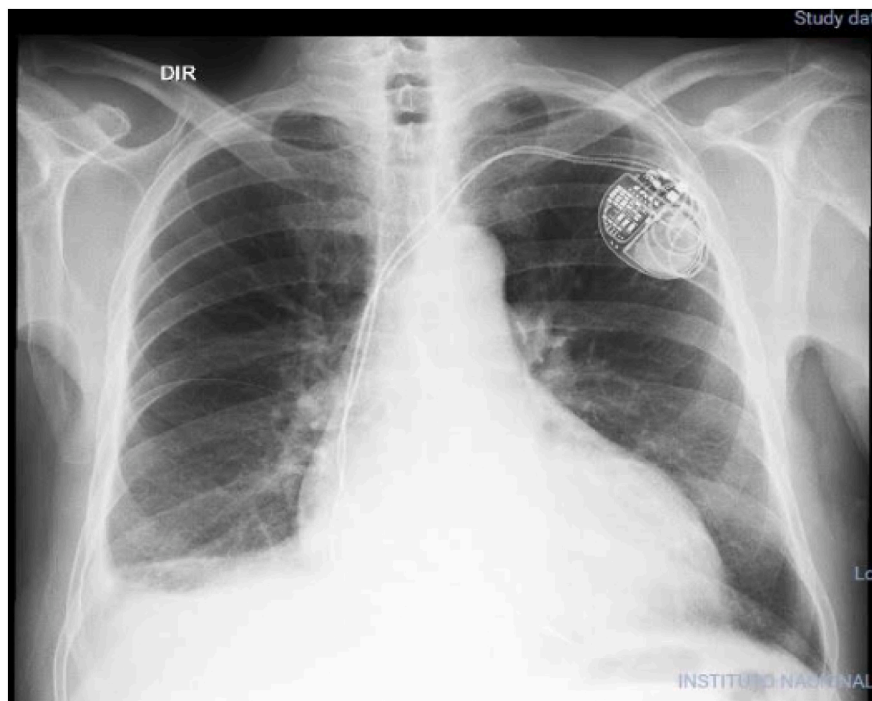


Fig. 1. Chest X-ray showing cardiomegaly and pleural effusion.

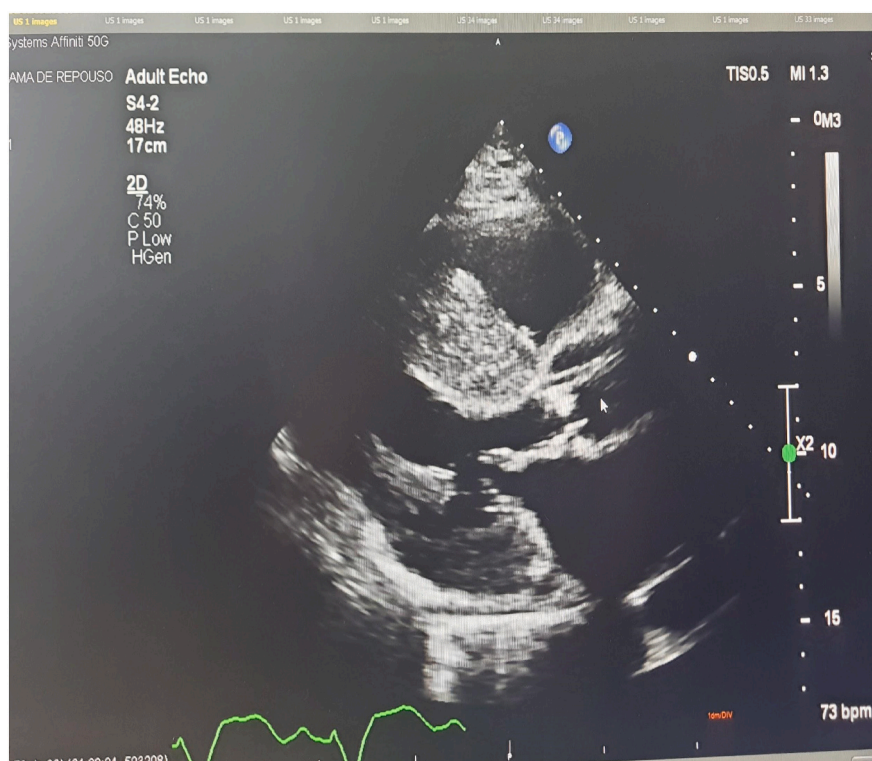


Fig. 2. TTE with aortic valve exhibited significant calcification.

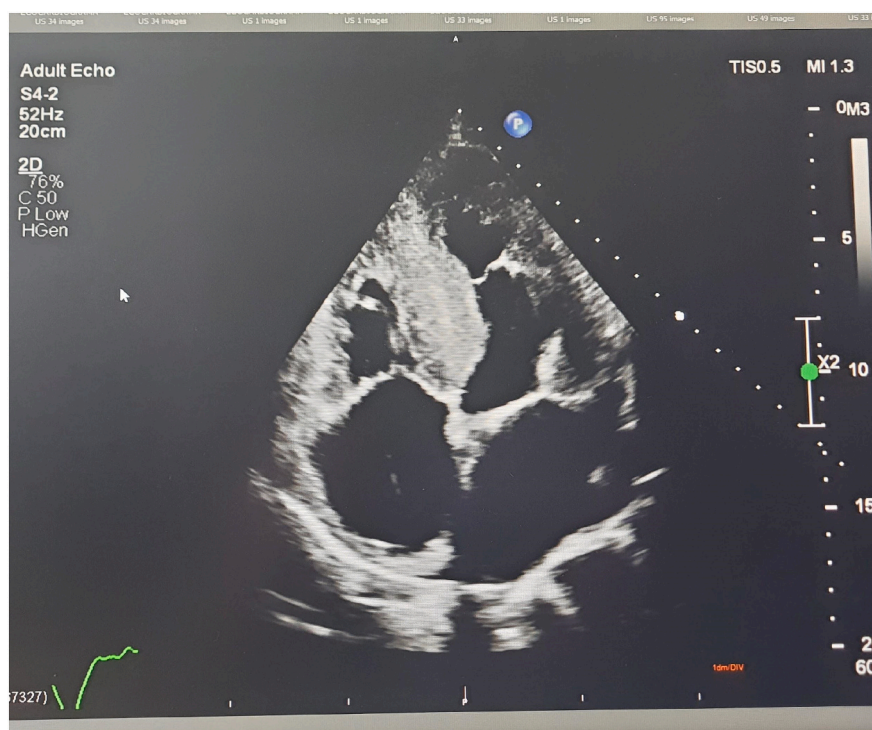


Fig. 3. TTE depicting enlargement of both atrial. The LV walls, especially the interventricular septum, show increased thickness and echogenicity, known as “myocardial sparkling”, indicative of infiltrative disease.

considering the associated risks of endomyocardial biopsy, the decision was made to perform genetic testing for mutations associated with hereditary forms of transthyretin amyloidosis (TTR). The material obtained from an oropharyngeal swab revealed heterozygosity for the variant Chr18: 31,595,169 T>C, which results in the substitution of the

amino acid phenylalanine at position 84 with leucine. This variant is considered pathogenic, leading to susceptibility to hereditary transthyretin-related amyloidosis, a genetically determined condition with autosomal dominant inheritance.

Thus, a noninvasive diagnosis of hereditary transthyretin cardiac

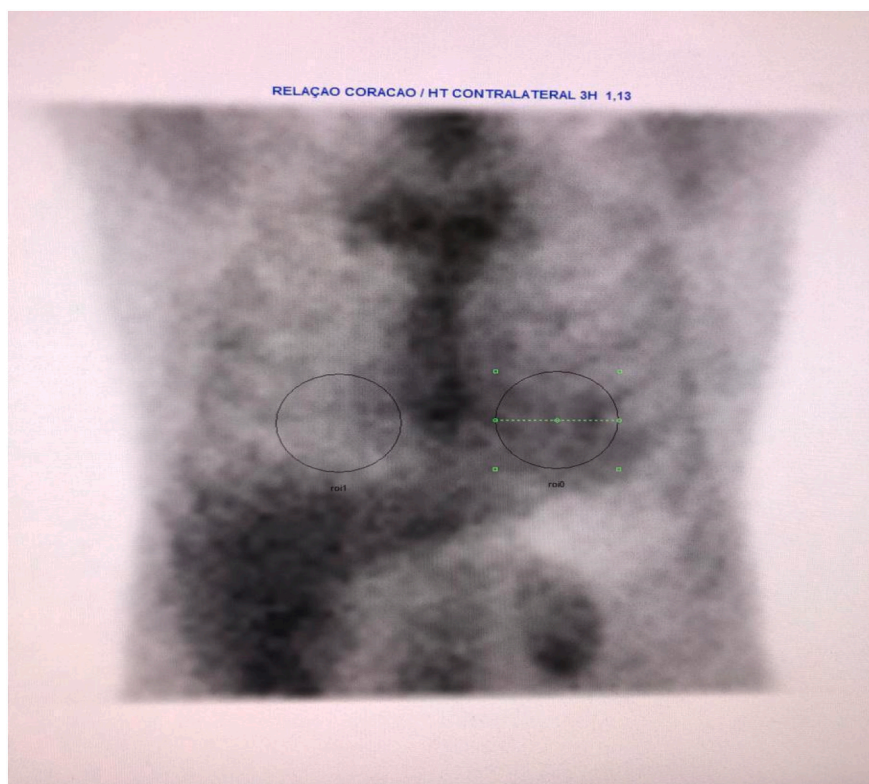


Fig. 4. Planar scintigraphy did not reveal abnormal tracer uptake.

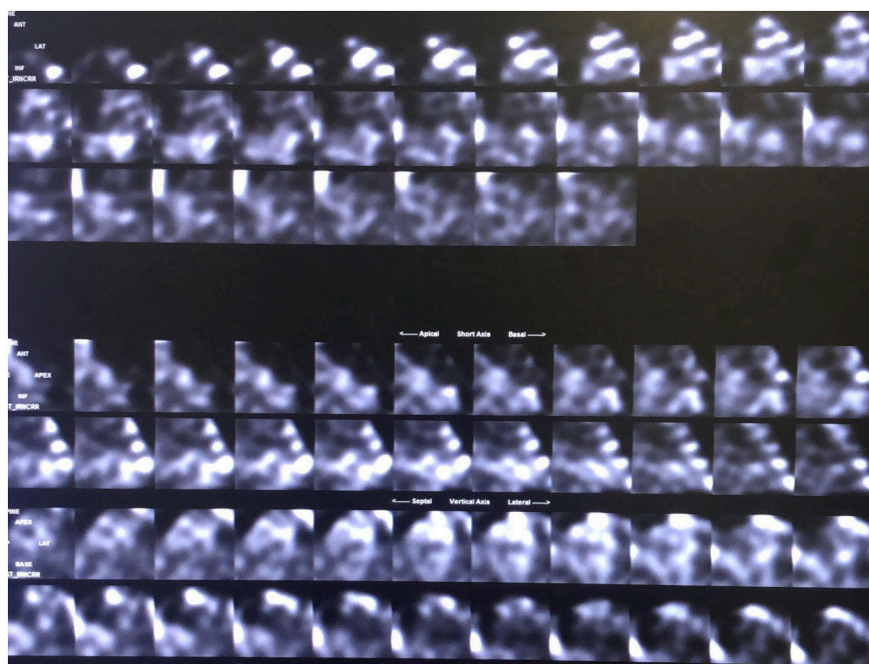
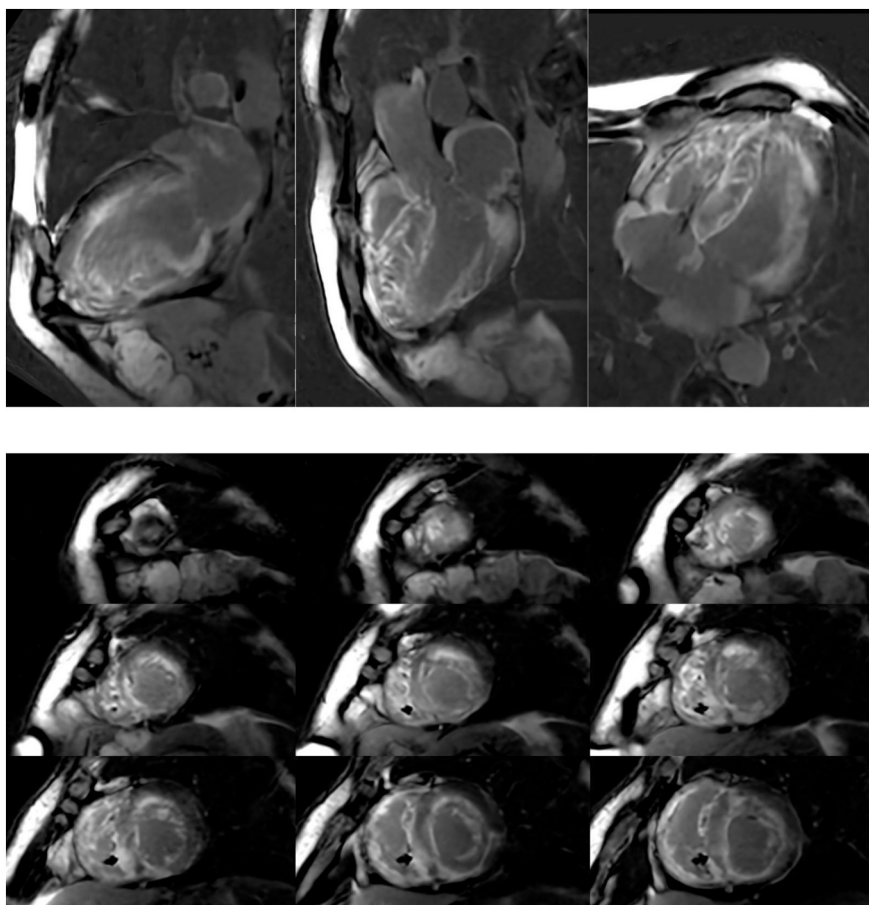


Fig. 5. Myocardial scintigraphy with 99 m technetium pyrophosphate illustrating the absence of abnormal tracer uptake with the presence of a blood pool inside the cardiac cavities visible in the SPECT images.

amyloidosis (CA-TTR) was established in this patient with severe symptomatic AS with negative scintigraphy results. Following discussion among the heart team and the calculation of prognostic scores, the estimated EUROSCORE II mortality rate for conventional surgical aortic valve replacement was approximately 24 % over 5 years. Consequently, the decision was made to pursue percutaneous treatment of AS with

transcatheter aortic valve implantation (TAVI) to improve the patient's symptoms. As part of the pre-TAVI protocol and as the patient refused to undergo an echocardiogram with dobutamine, computed tomography (CT) was performed to provide CT aortic valve calcium scoring, which confirmed a high calcium score of 2968 UA at the aortic valve (Fig. 8), supporting the diagnosis of severe AS.



Figs. 6 and 7. Cardiac magnetic resonance imaging (MRI) revealing extensive and heterogeneous late gadolinium enhancement within the myocardium in both ventricles and both atria. The enhancement pattern is a hallmark feature of infiltrative conditions, such as amyloidosis.

Cardiac catheterization revealed a severe lesion in the middle third of the left anterior descending artery (LAD) and occlusion of the right coronary artery.

Percutaneous intervention for the LAD lesion was scheduled during the same procedure as TAVI. On the day of the procedure, prior to its commencement, the patient experienced massive haematuria as a complication of an indwelling urinary catheter placement performed according to the department's protocol for patients with benign prostatic hyperplasia. Nevertheless, the decision was made to proceed with TAVI, although coronary disease was not addressed due to haematuria experienced in the operating room. Following the TAVI procedure, the patient was transferred to another hospital unit for follow-up with urology and was discharged after achieving clinical stability.

The patient is currently asymptomatic from a cardiovascular perspective and is classified as NYHA Functional Class I and he has been referred for outpatient follow-up at the Amyloidosis Referral Center in Rio de Janeiro at the Federal University of Rio de Janeiro, where he has been treated with tafamidis and educated about the importance of familial counselling.

2. Discussion

Amyloidosis is a disease characterized by the abnormal deposition of amyloid protein in various tissues, commonly affecting the heart. The most common forms include amyloidosis originating from deposits of immunoglobulin light chains (ALs) and transthyretin (ATTR), which can result from genetic mutations. ATTR can be classified as hereditary or mutant (hATTR) when associated with genetic mutations or as wild type (wtATTR) when not related to genetic mutations. The latter is more

commonly associated with ageing and was previously referred to as senile amyloidosis [1–4].

In CA, amyloid fibrils accumulate between cardiac myocytes, leading to impaired compliance, arrhythmias, and diastolic dysfunction. In advanced stages, CA is characterized as a restrictive cardiomyopathy that progresses to clinical heart failure [1,5,6]. The most common manifestation of CA -TTR is heart failure with a preserved ejection fraction [4,7,8].

Cardiomyopathy related to ATTR amyloidosis is increasingly recognized as a cause of heart failure in the elderly population. This disease is often identified at a late stage in the majority of cases, contributing to a poorer prognosis, with a survival rate of approximately 2–6 years following diagnosis or slightly longer in the case of wtATTR [4,6,9]. The delayed diagnosis can be attributed to a limited understanding of the disease, coupled with its diverse and nonspecific clinical manifestations until heart failure becomes established. A lack of awareness of available therapies and limited access to diagnostic methods also contribute to diagnostic delays [1,2,5].

Interestingly, in individuals of African descent over the age of 70, CA -TTR is twice as common as AL-related amyloidosis [6]. Additionally, with respect to age, autosomal-dominant hATTR amyloidosis is observed in slightly younger patients than the wild-type form of the disease.

>120 mutations leading to amyloid fibril deposition have been described, with the most common being Val122Ile, also known as the Afro-American mutation. This mutation primarily presents with cardiomyopathy. In contrast, in Europe and Japan, the endemic Val30Met mutation is associated with a predominance of polyneuropathy over cardiomyopathy [6,10,11]. The involvement of the median nerve in the



Fig. 8. CT revealing significant aortic calcification.

upper limbs, known as carpal tunnel syndrome, particularly when bilateral, is an important diagnostic clue and should raise suspicion of CA when accompanied by heart failure [12]. In the international THAOS study, 90 % of Brazilian patients had the Val30Met mutation, whereas other less frequent mutations included Ile107Val, Asp38Tyr, Val122Ile, and Val71Ala [11]. The Phe84Leu mutation (previously known as the Phe64Leu mutation) found in this patient is very rare and was reported only once previously in the THAOS study in Brazil [13].

AS is the most common valvular disease worldwide, affecting approximately 12 % of individuals over 75 years of age [14]. Severe AS is associated with CA in up to 16 % of cases [10,15]. This association may be due to the similar epidemiology of both diseases, which are more common in elderly adult men, or because the diseases contribute to each other's perpetuation, with AS leading to increased diastolic restriction or amyloidosis exacerbating stenosis by depositing amyloid fibrils in the valve [15–19].

According to the literature, patients with a combination of AS and CA are more symptomatic, have worse functional capacity, and experience a poorer prognosis with higher mortality than those with isolated AS [6,20]. These patients often exhibit a paradoxical low-flow low-gradient AS profile, including a valve area $\leq 1 \text{ cm}^2$, a mean LV/aorta gradient $<40 \text{ mmHg}$, and a left ventricular ejection fraction $>50 \%$. These patients have a worse prognosis than those with isolated AS [12,21]. As the disease progresses, the combination of severe CA and AS can lead to systolic dysfunction and the classical low-flow low-gradient profile, as observed in this patient. Notably, two findings that are considered frequent in isolated CA are much less common and lose specificity when comorbid with AS, namely, a high prevalence in males and apical preservation of longitudinal strain [18].

Regardless of genotype, identifying warning signs of phenotypes related to possible amyloidosis in association with AS is of the utmost importance. This is because, in addition to a worse prognosis, typical heart failure therapies may not be well tolerated by these patients [21].

The utilization of scores such as RAISE (Remodelling, Age, Injury, System, and Electrical), which include various clinical, electrocardiographic, echocardiographic, and blood biomarker parameters, can serve as a tool when amyloidosis is suspected [16,17].

Cardiac conduction abnormalities can be the first manifestation of the disease (7 %), and amyloid infiltration of the sinoatrial or atrio-ventricular node can lead to the indication for permanent pacemaker placement. Atrial arrhythmias are also common in these patients, with a high prevalence of atrial fibrillation (AF), and stroke is the first manifestation in many cases [7,22].

Regarding diagnostic methods, while endomyocardial biopsy with Congo red staining is still considered the gold standard for diagnosis, significant advancements have been made in recent years regarding the noninvasive diagnosis of CA [12,23]. Endomyocardial biopsy is an invasive method with potential risks. Conversely, biopsies from other extracardiac sites may have low accuracy in patients with CA-TTR [4]. Consequently, pyrophosphate scintigraphy and cardiac magnetic resonance are currently the most crucial imaging tests for definitive diagnosis.

Even before more sophisticated complementary tests are performed, the electrocardiogram itself can provide indications of amyloidosis. Low voltage or normal voltage despite echocardiographically detected hypertrophy can be indicative of amyloidosis, although these findings are nonspecific [4,5]. The presence of bundle branch block and conduction disturbances are also associated with the disease, and cardiac conduction abnormalities requiring pacemaker implantation can be the initial cardiac manifestation of amyloidosis, as observed in the reported patient [6,12].

In cases of suspected CA, all patients should undergo blood tests to assess the ratio of free light chains, as well as serum and urine protein electrophoresis and immunofixation [1,2,4]. AL amyloidosis has specific serum and urine markers, but these markers are lacking in ATTR CA, although some new serologic tests are under investigation [12].

Laboratory tests such as NT-proBNP measurements serve to assess the prognostic severity of heart failure and aid in distinguishing between AL and ATTR amyloidosis. In patients above 70 years of age, NT-proBNP levels <1430 are associated with the wtATTR phenotype [6]. However, troponin levels do not appear to differ significantly between phenotypes, although they are also related to prognosis.

Echocardiography can reveal diastolic dysfunction, interventricular septal thickening (especially exceeding 14 mm), biatrial enlargement, valvular and interatrial septal thickening, and “apical sparing” or “cherry on top” longitudinal strain, all of which contribute to diagnostic suspicion. The description of “sparkling” myocardium due to alterations in myocardial thickness and density is common. Global longitudinal strain assessment has proven to be superior and can be performed earlier than evaluation of the left ventricular ejection fraction, making it an important tool in the early diagnosis of CA involvement [8]. Nevertheless, no individual alteration is specific for diagnosis [12]. On echocardiography, CA -TTR can affect all cardiac structures through tissue infiltration, unlike chronic hypertension and AS, which can lead to myocardial hypertrophy with septal and other left ventricular wall thickening but does not involve other structures, such as the right ventricle (RV) and interatrial septum.

In cardiac MRI, late gadolinium enhancement with diffuse and circumferential distribution in the subendocardial or transmural space is supportive of the diagnosis of CA. This feature has prognostic value in CA and is essential for distinguishing extracellular amyloid deposition from diffuse fibrosis in patients with AS [24]. However, this enhancement is present in only approximately 25 % of patients. Late transmural enhancement is more common but can also be absent in 15 % of cases [22]. The transmural pattern is associated with a worse prognosis and higher mortality. In patients with CA, cardiac MRI can provide additional information associated with worse outcomes, such as the degree of myocardial hyperchogenicity, mitral deceleration time, right ventricular dilation, left ventricular ejection fraction, left ventricular wall thickness, and the myocardial performance index [24].

Myocardial scintigraphy has a sensitivity of 92 % and specificity of 95 % [25]. This allows for early and noninvasive diagnosis of ATTR. The radiotracer can bind to specific fragments of the TTR protein, predominantly occurring in the myocardium, due to the substantial amyloid content and its spatial arrangement in this tissue [12,26]. Cardiac scintigraphy is included in the algorithms for CA by cardiology societies in the United States and Europe [1,2]; however, despite its high specificity and sensitivity, a few mutations, such as Ser77Tyr and Phe64Leu, may not yield positive results [2,5,25,27,28]. This is the case for the patient's mutation, Phe84Leu (previously known as Phe64Leu), in the reported case. Scintigraphy is especially useful for distinguishing between different forms of CA, such as AL and ATTR [29]. This differentiation is crucial, as the various forms have distinct therapeutic approaches as well as prognostic implications [26].

Invasive diagnosis of CA -TTR is defined by biopsy of the affected tissue and histopathology revealing the presence of amyloid fibrils. A negative biopsy result does not exclude the disease since the collected tissue fragment may not have been ideal [22]. Immunohistochemistry is definitive, although it is less sensitive for recognizing light chains.

The performance of genetic tests for TTR gene sequencing is not only beneficial for confirming the diagnosis but also essential for the comprehensive assessment of patients already diagnosed with CA [30]. Distinguishing between hATTR and wtATTR is important for subsequent genetic counselling of the patient's first-degree relatives [30] and for guiding treatment decisions, as mRNA silencers are currently approved only for hATTR.

In treatment, the two main objectives are clinical support and slowing disease progression whenever possible. This involves managing heart failure once it is established while avoiding hypovolemia, as the restrictive pattern of CA can lead to a marked decrease in ventricular filling pressures and severe hypotension. Caution is necessary when beta-blockers are used in these patients because of the frequent

comorbidity of conduction disorders, especially wtATTR. Calcium channel antagonists and digoxin can bind to amyloid fibrils, increasing their toxic potential. Therefore, they are not recommended for these patients [6,8]. In cases where heart rate control is needed for AF, amiodarone is the preferred drug, and the use of nonvitamin K antagonist oral anticoagulants (NOACs) should be initiated regardless of the CHA2DS2-VASc score [8]. Unlike patients with other causes of heart failure, there is no established benefit of the use of beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers in patients with CA [22].

A consensus has not yet been reached regarding the management of concomitant diseases such as AS and CA. Mortality is reduced within 12 months when patients with severe AS and amyloidosis undergo transcatheter aortic valve implantation (TAVI); however, hospitalization rates for decompensated heart failure remain high after the procedure [18]. Moreover, the combination of AS and CA has a greater tendency to require pacemaker implantation after TAVI [15,31]. Although the benefit of valve intervention in these patients, specifically TAVI, has historically been debated as futile [20,31], more recent evidence suggests potential benefits of valve intervention, particularly in improving symptoms and quality of life for these patients [1,8,15,31–34]. The question remains regarding whether disease-modifying drugs (DMDs) should be administered before or after TAVI.

In the case of coronary artery disease, percutaneous treatment with stents should be prioritized over coronary artery bypass surgery, as these patients often have increased surgical risk.

Regarding devices for arrhythmia treatment, both permanent pacemakers and implantable cardioverter defibrillators have indications for secondary prophylaxis per specific guidelines, but there is still no proven benefit for their use as primary prophylaxis in CA patients [1,2].

The specific treatment of CA currently relies on the use of tafamidis, an orally administered transthyretin stabilizer approved by the European Medicines Agency and by the FDA in the U.S. Tafamidis is known to delay neurological disease progression. Recent data indicate the efficacy of this drug in cardiovascular disease as well [35]. Ongoing studies are evaluating the effectiveness and safety of other drugs for amyloidosis, including other stabilizers, drugs that inhibit TTR synthesis by the liver and even RNA-modifying drugs for the protein. Other studies are exploring drugs that assist in the elimination of amyloid deposits [6,8].

Early clinical recognition and diagnosis of CA-TTR are crucial, especially given the recent increase in diagnostic test availability and the emergence of new disease-modifying therapies. Clinical scores such as the RAISE score can help determine which patients should undergo CA screening and guide further investigations, regardless of previously established algorithms. While having a diagnostic algorithm is important, it is essential to recognize that diagnosis should be pursued even in the presence of negative complementary tests if there is a strong clinical and familial history. The diagnostic evaluation of elderly patients with AS and typical CA findings should be comprehensive, as ATTR has proven to be more common than previously assumed. The therapeutic approach involving percutaneous procedures in these CA patients, including the use of TAVI in cases of associated AS, should be discussed with a heart team, as it has the potential to have a favourable impact on both the quantity and quality of life of patients.

3. Lay summary

Early clinical recognition and diagnosis of CA-TTR are crucial, especially given the recent increase in diagnostic test availability and the emergence of new disease modifiers. While having a diagnostic algorithm is important, it is essential to recognize that diagnosis should be pursued even in the presence of negative complementary tests if there is a strong clinical and familial history. The diagnostic evaluation of elderly patients with AS and typical CA findings should be comprehensive, as ATTR has proven to be more common than previously assumed. The therapeutic approach involving percutaneous procedures in these

CA patients, including the use of TAVI in cases of associated AS, should be discussed with a heart team, as it has the potential to have a favourable impact on both the quantity and quality of life of patients.

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The hospital gave ethical approval for this manuscript.

Informed consent

Informed consent terms were used to perform the exams.

CRedit authorship contribution statement

Gabriela Carvalho Monnerat Magalhães: Writing – original draft, Investigation, Conceptualization. **Luciana Coutinho Bezerra:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Beny Binensztok:** Writing – original draft, Investigation, Conceptualization. **Maysa Ramos Vilela:** Writing – original draft. **Ellen Fernanda das Neves Braga:** Writing – original draft. **Adriana Soares Xavier de Brito:** Writing – original draft, Data curation. **Gabriel Cordeiro Camargo:** Data curation. **Luiz Felipe Camillis:** Conceptualization. **Helena Cramer Veiga Rey:** Project administration. **Clara Weksler:** Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] M.M. Kittleson, F.L. Ruberg, A.V. Ambardekar, T.H. Brannagan, R.K. Cheng, J. O. Clarke, et al., 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the american college of cardiology solution set oversight committee, *J. Am. Coll. Cardiol.* 81 (2023) 1076–1126.
- [2] P. Garcia-Pavia, C. Rapezzi, Y. Adler, M. Arad, C. Basso, A. Brucato, et al., Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC working group on myocardial and pericardial diseases, *Eur. Heart J.* 42 (2021) 1554–1568.
- [3] T.A. Treibel, M. Fontana, J.A. Gilbertson, S. Castelletti, S.K. White, P.R. Scully, et al., Occult transthyretin cardiac amyloid in severe calcific aortic stenosis: prevalence and prognosis in patients undergoing surgical aortic valve replacement, *Circ. Cardiovasc. Imaging* 9 (2016) e005066.
- [4] R.M. Witteles, S. Bokhari, T. Damsy, P.M. Elliott, R.H. Falk, N.M. Fine, et al., Screening for transthyretin amyloid cardiomyopathy in everyday practice, *JACC Heart Fail.* 7 (2019) 709–716.
- [5] M.S. Maurer, S. Bokhari, T. Damsy, 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) e006075.
- [6] A. Castaño, B.M. Drachman, D. Judge, M.S. Maurer, Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs, *Heart Fail. Rev.* 20 (2015) 163–178.
- [7] E. González-López, M. Gallego-Delgado, G. Guzzo-Merello, F.J. de Haro-Del Moral, M. Cobo-Marcos, C. Robles, et al., Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction, *Eur. Heart J.* 36 (2015) 2585–2594.
- [8] M. Raval, S. Siddiq, K. Sharma, L. Sanghvi, A. Jain, S. Patel, et al., A review of recent advances in the diagnosis of cardiac amyloidosis, treatment of its cardiac complications, and disease-modifying therapies, *F1000Res* 12 (2023) 192.
- [9] T. Lane, M. Fontana, A. Martinez-Naharro, C.C. Quarta, C.J. Whelan, A. Petrie, et al., Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis, *Circulation* 140 (2019) 16–26.
- [10] A. Castaño, D.L. Narotsky, N. Hamid, O.K. Khalique, R. Morgenstern, A. DeLuca, et al., Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement, *Eur. Heart J.* 38 (2017) 2879–2887.
- [11] M.W. Cruz, M.V. Pinto, L.F. Pinto, R. Gervais, M. Dias, C. Perez, et al., Baseline disease characteristics in Brazilian patients enrolled in transthyretin amyloidosis outcome survey (THAOS), *Arq. Neuropsiquiatr.* 77 (2019) 96–100.
- [12] A.S. Hafeez, A.A. Bavry, Diagnosis of transthyretin amyloid cardiomyopathy, *Cardiol. Ther.* 9 (2020) 85–95.
- [13] L. Gentile, I. Diemberger, V. Plante-Bordeneuve, A. Mazzeo, A. Dori, M. Luigetti, et al., Phenotypic characteristics of F64L, I68L, I107V, and S77Y ATTRv genotypes from the transthyretin amyloidosis outcomes survey (THAOS), *PLoS One* 19 (1) (2024) e0292435.
- [14] B. Lindman, C. Otto, R. Bonow, Valvopatía aórtica – Braunwald: tratado de doenças cardiovasculares, 2022.
- [15] J.M. Riley, J. Junarta, W. Ullah, M.U. Siddiqui, A. Anzelmi, M. Ruge, et al., Transcatheter aortic valve implantation in cardiac amyloidosis and aortic stenosis, *Am. J. Cardiol.* 198 (2023) 101–107.
- [16] P. Pibarot, P. Lancellotti, J. Narula, Concomitant cardiac amyloidosis in severe aortic stenosis: the trojan horse? *J. Am. Coll. Cardiol.* 77 (2021) 140–143.
- [17] C. Nitsche, P.R. Scully, K.P. Patel, A.A. Kammerlander, M. Koschutnik, C. Dona, et al., Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis, *J. Am. Coll. Cardiol.* 77 (2021) 128–139.
- [18] H. Rosenblum, A. Masri, D.L. Narotsky, J. Goldsmith, N. Hamid, R.T. Hahn, et al., Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis, *Eur. J. Heart Fail.* 23 (2021) 250–258.
- [19] C. Rapezzi, F. Giannini, G. Campo, Aortic stenosis, transcatheter aortic valve replacement and transthyretin cardiac amyloidosis: are we progressively unraveling the tangle? *Eur. J. Heart Fail.* 23 (2021) 259–263.
- [20] J. Ternacle, L. Kráp, D. Mohy, 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) 2638–2651.
- [21] M.B. Leon, C.R. Smith, M. Mack, D.C. Miller, J.W. Moses, L.G. Svensson, et al., Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery, *N. Engl. J. Med.* 363 (2010) 1597–1607.
- [22] E. González-López, Á. López-Sainz, P. Garcia-Pavia, Diagnosis and treatment of transthyretin cardiac amyloidosis, Progress and hope. *Rev Esp Cardiol (Engl Ed)* 70 (2017) 991–1004.
- [23] J.L. Cavalcante, S. Rijal, I. Abdelkarim, A.D. Althouse, M.S. Sharbaugh, Y. Fridman, et al., Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis, *J. Cardiovasc. Magn. Reson.* 19 (2017) 98.
- [24] B.A. Austin, W.H. Tang, E.R. Rodriguez, C. Tan, S.D. Flamm, D.O. Taylor, et al., Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis, *JACC Cardiovasc. Imaging* 2 (2009) 1369–1377.
- [25] N. Tahara, O. Lairez, J. Endo, A. Okada, M. Ueda, T. Ishii, et al., (99m) technetium-pyrophosphate scintigraphy: a practical guide for early diagnosis of transthyretin amyloid cardiomyopathy, *ESC Heart Fail.* 9 (2022) 251–262.
- [26] E. Perugini, P.L. Guidalotti, F. Salvi, R.M. Cooke, C. Pettinato, L. Riva, et al., Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy, *J. Am. Coll. Cardiol.* 46 (2005) 1076–1084.
- [27] M.B. Musumeci, F. Cappelli, D. Russo, G. Tini, M. Canepa, A. Milandri, et al., Low sensitivity of bone scintigraphy in detecting Phe64Leu mutation-related transthyretin cardiac amyloidosis, *JACC Cardiovasc. Imaging* 13 (2020) 1314–1321.
- [28] M. Hanna, F.L. Ruberg, M.S. Maurer, A. Dispenzieri, S. Dorbala, R.H. Falk, et al., Cardiac scintigraphy with technetium-99m-labeled bone-seeking tracers for suspected amyloidosis: JACC review topic of the week, *J. Am. Coll. Cardiol.* 75 (2020) 2851–2862.
- [29] J.D. Gillmore, M.S. Maurer, R.H. Falk, G. Merlini, T. Damsy, A. Dispenzieri, et al., Nonbiopsy diagnosis of cardiac transthyretin amyloidosis, *Circulation* 133 (2016) 2404–2412.
- [30] A. Sousa, O. Moldovan, A. Lebreiro, M. Bourbon, N. António, Q. Rato, et al., Recomendações para a realização de testes genéticos em cardiologia – revisão das principais diretrizes internacionais, *Rev. Port. Cardiol.* 39 (2020) 597–610.
- [31] F. Cannata, M. Chiarito, G. Pinto, A. Villaschi, J. Sanz-Sánchez, F. Fazzari, et al., Transcatheter aortic valve replacement in aortic stenosis and cardiac amyloidosis: a systematic review and meta-analysis, *ESC Heart Fail.* 9 (2022) 3188–3197.
- [32] T. Damsy, 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) e000289.
- [33] D. de Campos, C. Saleiro, A. Botelho, M. Costa, L. Gonçalves, R. Teixeira, Aortic valve intervention for aortic stenosis and cardiac amyloidosis: a systematic review and meta-analysis, *Future Cardiol.* 18 (2022) 477–486.
- [34] Cappelli F, Peretto F, Martone R, di Mario C. Cardiac amyloidosis in patients undergoing TAVR: why we need to think about it. *Cardiovasc. Revasc. Med.*
- [35] M.S. Maurer, J. Schwartz, B. Gundapaneni, P. Elliot, et al., Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy, *N. Engl. J. Med.* 379 (2018) 1007–1016, <https://doi.org/10.1056/NEJMoa1805689>.