ESC European Society of Cardiology

European Heart Journal - Case Reports (2025) **9**, ytaf633
https://doi.org/10.1093/ehjcr/ytaf633

GRAND ROUND
Inherited cardiac conditions/cardiomyopathies

Atypical gastrointestinal presentation of hereditary transthyretin amyloidosis: a case report highlighting the diagnostic challenge

Lilaf Abdulmajid [1]*, Lucas Wauters[2,3], Tim Vanuytsel[2,3], Gert De Hertogh[4,5], Benjamin Peters[6,7], and Philippe Timmermans Jr[1,7]

[1]Department of Cardiology, Heart Centre Hasselt, Jessa Hospital, Stadsomvaart 11, Hasselt 3500, Belgium; [2]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium; [3]Translational Research Center for Gastrointestinal Disorders (TRAGID), Department of Chronic Diseases and Metabolism (ChroMeta), University of Leuven, Herestraat 49, 3000 Leuven, Belgium; [4]Laboratory of Pathology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium; [5]Department of Imaging and Pathology, University of Leuven, Herestraat 49, 3000 Leuven, Belgium; [6]Department of Radiology, Jessa Hospital, Stadsomvaart 11, Hasselt 3500, Belgium; and [7]Faculty of Medicine and Life Sciences, Hasselt University, Agoralaan Gebouw D, Hasselt BE3590 Diepenbeek, Belgium

Received 9 July 2025; revised 17 September 2025; accepted 22 November 2025; online publish-ahead-of-print 29 November 2025

Background Hereditary transthyretin amyloidosis (ATTR) is a rare, progressive multisystem disease, often underdiagnosed due to its heterogeneous presentation. This case highlights an atypical presentation of ATTR amyloidosis dominated by gastrointestinal symptoms and the diagnostic pitfalls associated with certain genetic subtypes that may escape standard imaging modalities.

Case summary We present a 68-year-old man with severe gastrointestinal symptoms and extreme weight loss, over a prolonged period. Initial investigations were inconclusive across multiple centres. A deep intestinal biopsy eventually revealed amyloid deposition, and subsequent genetic testing confirmed hereditary ATTR amyloidosis. Cardiac magnetic resonance imaging revealed myocardial involvement despite a negative 99mTc-HDP scintigraphy. The patient was referred for targeted therapy.

Discussion This case underscores the need for high clinical suspicion and a multidisciplinary approach when encountering unexplained gastrointestinal and cardiac symptoms. It also demonstrates the value of the European Society of Cardiology guidelines as a reliable reference point for guiding further management when diagnostic uncertainty arises.

Keywords Case report • Hereditary transthyretin amyloidosis • Gastrointestinal symptoms • Unexplained weight loss • Diagnostic delay • Cardiac involvement

ESC curriculum 2.3 Cardiac magnetic resonance • 6.5 Cardiomyopathy

Learning points

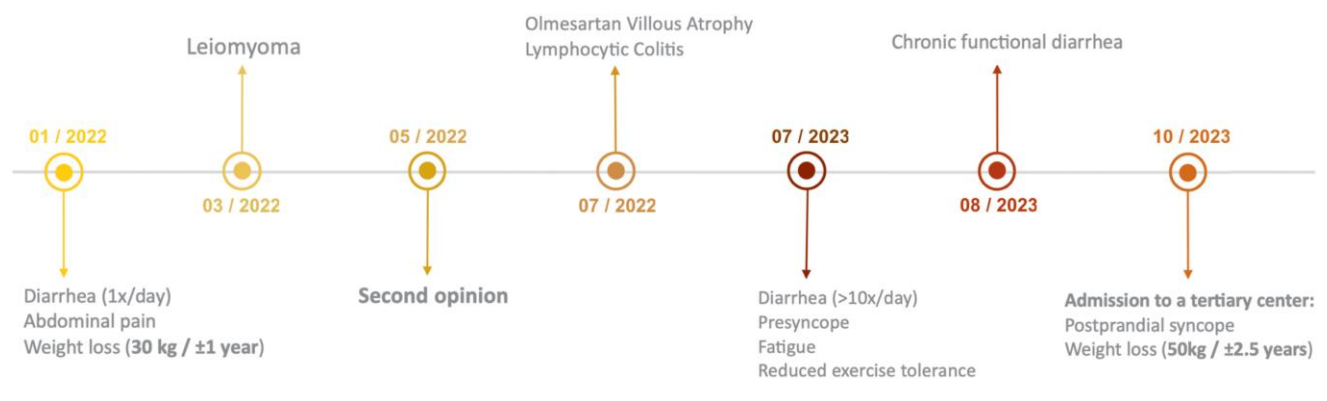
- Transthyretin amyloidosis (ATTR) can present with predominant gastrointestinal (GI) symptoms.
- A 99mTC scan may be negative in certain genetic subtypes of ATTR amyloidosis.
- Advanced imaging such as cardiac magnetic resonance imaging and molecular diagnostics such as genetic testing are important for diagnosing ATTR amyloidosis and guiding targeted therapy.
- For GI biopsies, deep tissue sampling is essential for diagnosing ATTR amyloidosis.

* Corresponding author. Email: lilaf_abdulmajid@hotmail.com
Handling Editor: Takeshi Kitai
Peer-reviewers: Ana Devesa; Toru Kubo
Compliance Editor: Deepti Ranganathan

Introduction

Hereditary transthyretin amyloidosis (ATTR) is a rare, autosomal dominant systemic disease characterized by extracellular deposition of misfolded transthyretin protein.[1] While cardiac and neurological manifestations are well recognized, gastrointestinal (GI) involvement is often underappreciated and can precede other symptoms.[2] Early recognition is essential, as new therapies can halt disease progression.[3] We report a case of hereditary ATTR amyloidosis with an atypical predominant GI presentation, highlighting diagnostic pitfalls and the importance of a multidisciplinary approach.

Summary figure



Delayed diagnosis in hereditary ATTR amyloidosis: a 2-year diagnostic odyssey across multiple gastroenterology centres

Case presentation

A 68-year-old man from a second-generation Italian immigrant family presented in January 2022 with abdominal pain, diarrhoea, and significant weight loss. His medical history included curative resection for colon adenocarcinoma in 2016 and transurethral resection of the prostate in 2020. His regular medications were acetylsalicylic acid (for primary prevention), olmesartan/amlodipine, and simvastatin.

Initial investigations, including computed tomography (CT), gastroscopy, and endoscopic ultrasound (EUS), revealed a 15 mm submucosal lesion in the distal oesophagus/cardia. Biopsies indicated a leiomyoma; however, this finding did not adequately explain the patient's symptoms. A watchful waiting approach, combined with symptomatic treatment, was initiated.

As symptoms persisted, the patient was referred for a second opinion in May 2022. Further diagnostic work-up, including sigmoidoscopy and positron emission tomography–computed tomography (PET–CT), yielded negative results. Olmesartan-induced enteropathy was considered as a provisional diagnosis, and his antihypertensive therapy was switched to ramipril.

In July 2023, the patient presented to the emergency department with severe diarrhoea (more than 10 episodes per day), orthostatic presyncope, fatigue, and markedly reduced exercise tolerance. Repeat CT imaging demonstrated evidence of third spacing, including bilateral pleural effusions and subcutaneous oedema. No cardiac work-up was performed at that time. Given the patient's severe malnutrition with profound weight loss, the effusions were presumed to be of non-cardiac origin, with hypoalbuminaemia or protein-losing enteropathy being considered. Despite extensive other investigations, no underlying cause was identified, and a working diagnosis of chronic functional diarrhoea was established.

By October 2023, he was referred to a tertiary care centre due to postprandial syncope and a total weight loss of ∼50 kg over 2 years (weight at presentation, 60 kg). A 72-h faecal collection demonstrated high stool volume [766 g; upper limit of normal (ULN), 200 g] with significant faecal bile acid loss (4.26 mmol/d, ULN 1.11 mmol/d), suggestive of malabsorption. Gastroduodenoscopy and colonoscopy with biopsies were performed.

Histopathological analysis of duodenal biopsies showed amyloid deposits in submucosal blood vessels. Congo red staining of surgically obtained rectal biopsies confirmed amyloid deposition, displaying a characteristic amorphous, orange–pink material in a perivascular pattern (*Figure 1A*), with apple-green birefringence under polarized light. Immunohistochemistry was positive for transthyretin (TTR) (*Figure 1B*), confirming a diagnosis of ATTR amyloidosis. Serum and urine protein electrophoresis revealed no monoclonal proteins, excluding light-chain (AL) amyloidosis.

Given the diagnosis of intestinal ATTR amyloidosis and symptoms of reduced exercise tolerance, cardiac involvement was assessed. Transthoracic echocardiography revealed severe concentric left ventricular hypertrophy and reduced global longitudinal strain with apical sparing (*Figure 2*), which is highly suggestive of cardiac amyloidosis. At the time of examination, no pleural effusions were present, and there were no echocardiographic signs of elevated filling pressures; the central venous pressure was normal, while pulmonary artery pressures (PAPs) could not be reliably estimated. Electrocardiogram demonstrated low QRS-complex voltages in the peripheral leads together with a pseudo-infarction pattern, characterized by a QS complex in V1–V2 and a small R wave in V3. These features may reflect loss of myocardial cells and amyloid-related hypertrophy due to fibril deposition,[4] thereby supporting the diagnosis of cardiac amyloidosis (*Figure 3*). A 99mTc scintigraphy using hydroxymethylene diphosphonate (HDP) was performed to confirm this diagnosis. However, the scan was negative (Perugini Grade 0) (*Figure 4*). Nonetheless, clinical suspicion for cardiac amyloidosis remained high.

In accordance with the 2023 European Society of Cardiology (ESC) cardiomyopathy guidelines,[5] cardiac magnetic resonance imaging (MRI) was performed. It revealed diffuse non-ischaemic myocardial fibrosis with transmural involvement of both ventricles, elevated native T1 values (1160 ms; ULN 1025 ms), and increased extracellular volume fraction (47.6%; ULN < 29%)—findings strongly suggestive of cardiac amyloidosis (*Figure 5*).

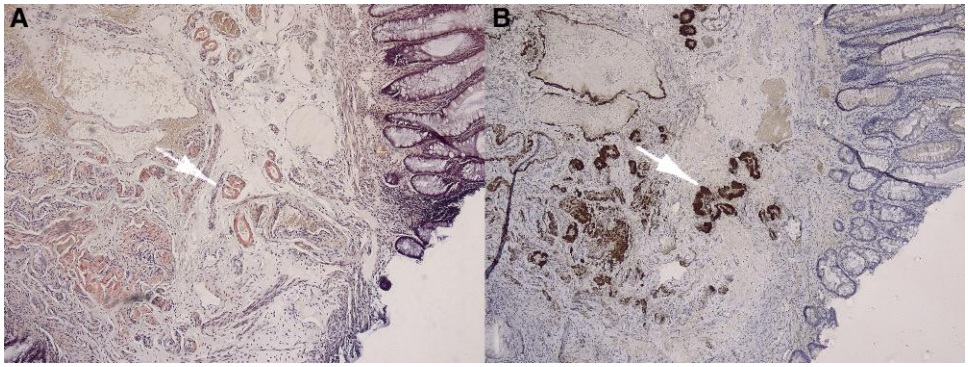


Figure 1 Congo red staining of rectal biopsy showing amyloid deposition in submucosal vessel walls (*A*) and immunohistochemistry positive transthyretin, confirming the diagnosis of transthyretin amyloidosis (*B*).

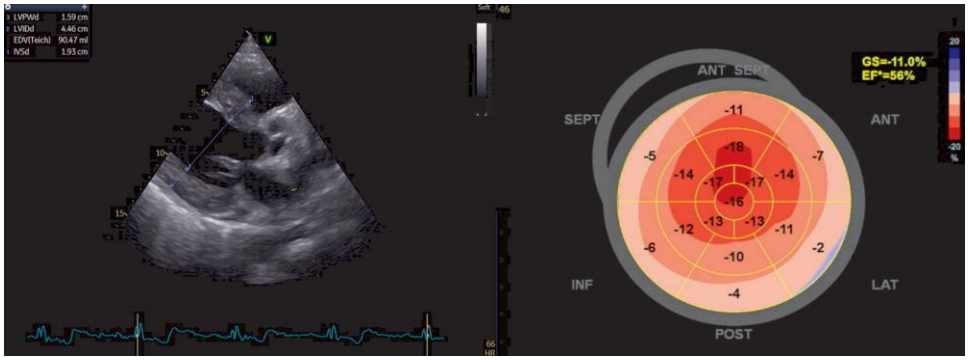


Figure 2 Transthoracic echocardiography demonstrating marked concentric left ventricular hypertrophy (interventricular septum, 19.3 mm; left ventricular end-diastolic diameter, 44.6 mm; posterior wall thickness, 15.9 mm) and reduced global longitudinal strain with apical sparing, findings highly suggestive of cardiac amyloidosis.

Treatment with the transthyretin stabilizer tafamidis (61 mg daily) was initiated. As there were no clinical signs of congestive heart failure, no specific heart failure therapy was started; supportive treatment for GI symptoms was continued. Ribonucleic acid (RNA) interference therapy was deferred pending neurological evaluation, as per national reimbursement criteria in Belgium.

Genetic testing identified a pathogenic variant in the *TTR* gene (c.250T>C, p.Phe84Leu). Annual follow-up with echocardiography and Holter monitoring was arranged.

His 32-year-old identical twin sons were also found to carry the same *TTR* mutation but remain asymptomatic, with negative 99mTc-HDP scintigraphy and cardiac MRI. They are undergoing regular clinical surveillance.

Discussion

This case highlights the diagnostic challenges associated with hereditary ATTR amyloidosis, particularly in patients carrying the p.Phe84Leu variant of the *TTR* gene. This mutation is associated with a late-onset sensorimotor neuropathy, with cardiac involvement occurring later in the disease course. While it is particularly prevalent in Southern Italy, its occurrence has also been reported in other regions of the country, likely because of internal migration patterns.[6]

Due to its late onset, incomplete penetrance, and often non-specific initial symptoms, this genotype is frequently associated with prolonged diagnostic delays. Moreover, amyloid derived from this *TTR* variant tends to demonstrate poor affinity for Congo red staining and limited uptake on bone scintigraphy with technetium-labelled tracers. This can result in false-negative biopsy findings and a mismatch between structural pathology and nuclear imaging, thereby complicating both diagnosis and disease monitoring.[6–8]

In addition to the well-described neurological and cardiac features, GI symptoms may represent an early and often underrecognized manifestation of hereditary ATTR amyloidosis. In a study by Wixner *et al.*,[2] GI symptoms were reported in 63% of hereditary ATTR patients, compared to 15% of patients with wild-type ATTR, with unintentional weight loss and early satiety being the most common complaints. Notably, symptom burden was shown to increase with advancing disease stage.

In the present case, predominant GI symptoms masked underlying cardiac involvement. This underscores the importance of considering amyloidosis in patients with unexplained GI complaints and signs of systemic disease.

Histopathological diagnosis via GI biopsy also presents unique challenges. Freudenthaler *et al.*[9] analysed over 600 GI biopsies and found ATTR to be the second most common amyloid type after AL, with a

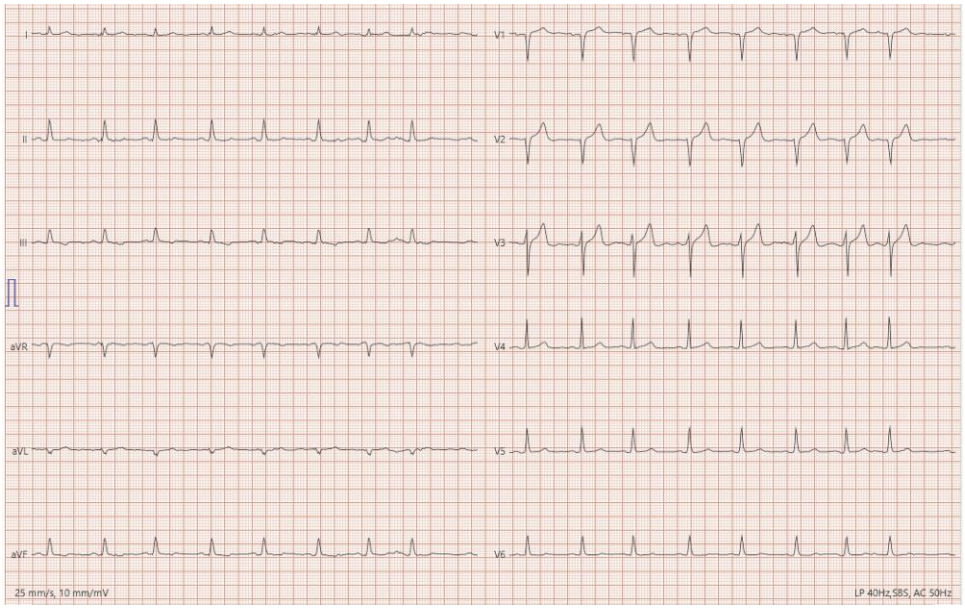


Figure 3 Electrocardiogram demonstrated low QRS-complex voltages in the peripheral leads together with a pseudo-infarction pattern, characterized by a QS complex in V1–V2 and a small R wave in V3.

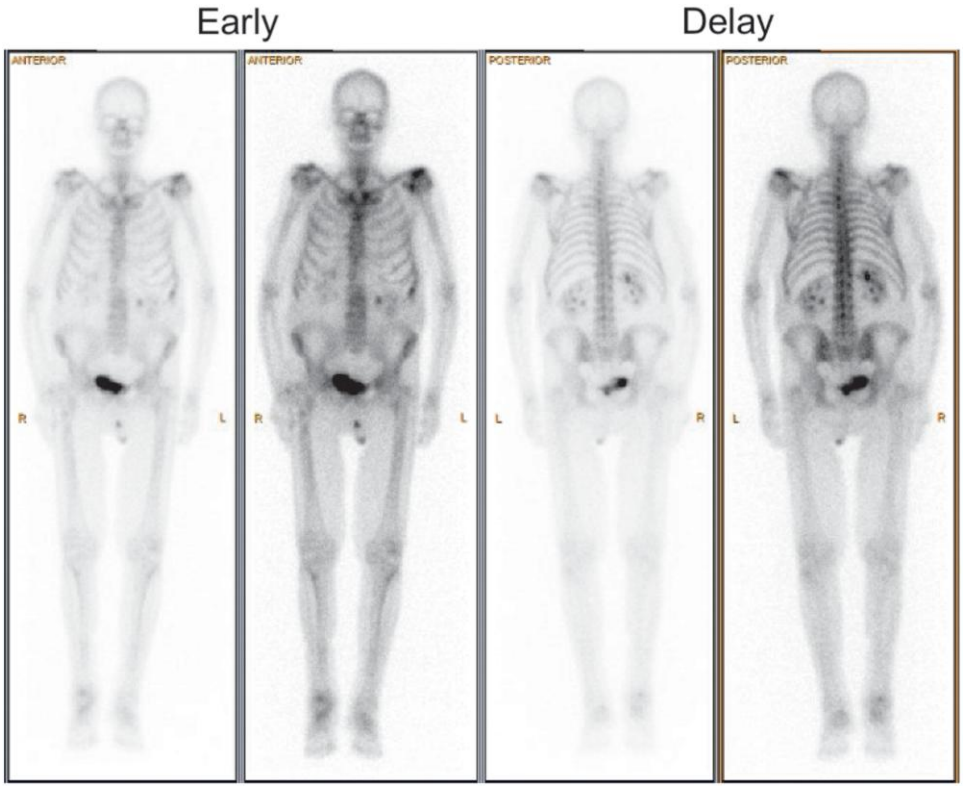


Figure 4 Perugini Grade 0 myocardial tracer uptake observed on 99mTc scan.

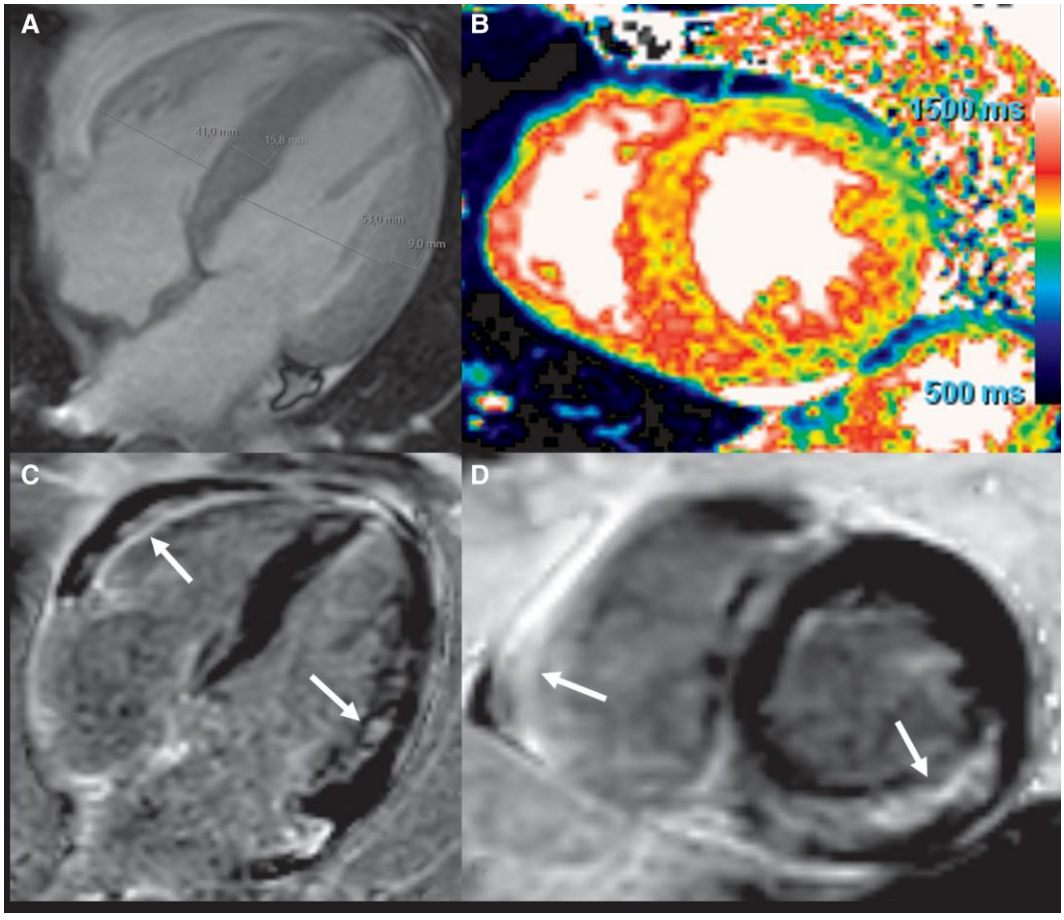


Figure 5 (*A*) Four-chamber cine image demonstrating increased myocardial wall thickness, indicative of left ventricular hypertrophy. The septal thickness measured 15.8 mm and left ventricular lateral wall thickness 9.0 mm, with an end-diastolic left ventricular diameter of 53.0 mm and a right ventricular diameter of 41.0 mm. (*B*) Short-axis T1 mapping image showing diffusely elevated native T1 values, most pronounced in the mid-ventricular septum (1160 ms; upper limit of normal, 1025 ms), consistent with diffuse myocardial involvement. (*C*) Four-chamber late gadolinium enhancement image revealing diffuse patchy mid-wall fibrosis in the basal to mid-ventricular lateral wall (arrow). (*D*) Short-axis late gadolinium enhancement image demonstrating transmural fibrosis involving the free lateral wall of the right ventricle, as well as the inferior to inferolateral segments of the left ventricle.

mean prevalence of 15.7%. Detection rates increased distally in the GI tract—from 9.8% in gastric samples to 20.5% in rectal biopsies. Amyloid deposits were most frequently located in the submucosa, primarily within vascular structures (99%), explaining why superficial biopsies—as in this case—may miss the diagnosis.

Late gadolinium enhancement (LGE) cardiac magnetic resonance typically reveals diffuse subendocardial or transmural enhancement in ATTR amyloidosis. However, focal or patchy intramyocardial LGE has also been reported, reflecting heterogeneous amyloid deposition patterns.[10–12] Specific LGE patterns linked to different hATTR mutations, including p.Phe84Leu, have not been clearly established. In the present case, LGE was observed in the inferolateral and inferior segments of the left ventricle as well as in the free lateral wall of the right ventricle, demonstrating a combination of mid-wall and transmural involvement. These findings likely reflect regional amyloid infiltration and may represent a mutation-dependent or disease stage–dependent phenotype. Further studies are needed to clarify the relationship between specific mutations and cardiac imaging phenotypes.

Finally, although 99mTc-labeled bone scintigraphy is a cornerstone in the non-invasive diagnosis of cardiac ATTR amyloidosis, its sensitivity is highly mutation dependent. Variants such as p.Val50Met, p.Ser97Tyr, and p.Phe84Leu are known to yield negative scintigraphy results, underscoring the need for molecular confirmation in clinically suspected cases.[13] This limitation was also reflected in our patient, in whom the 99mTc-HDP scan was negative despite clinical suspicion and confirmed genetic diagnosis.

Alternative nuclear imaging techniques have been investigated to address these diagnostic challenges. Although 99mTc-HDP generally provides high sensitivity for cardiac ATTR amyloidosis, comparable to other bone tracers such as 99mTc-DPD and 99mTc-PYP, certain mutations including p.Phe84Leu may still yield false-negative results even with HDP scintigraphy.[14] Musumeci *et al.* reported a notably low sensitivity of bone scintigraphy in patients carrying the p.Phe64Leu *TTR* mutation. The exact mechanism remains unclear, but several hypotheses have been proposed. One possibility is that calcium content within amyloid deposits affects tracer uptake. Another proposed determinant is the biochemical composition of the amyloid fibrils, which are broadly categorized as Type A (a mixture of C-terminal fragments and full-length transthyretin) or Type B (full-length transthyretin only). Observational data suggest that patients with Type B fibrils—a pattern reported in some carriers of the p.Phe64Leu variant—frequently exhibit absent or minimal bone-tracer uptake despite significant histologic

amyloid infiltration. These findings suggest that structural and biochemical properties of amyloid deposits can affect tracer binding and, consequently, the sensitivity of bone scintigraphy. Nevertheless, these remain associative data and further studies are required to establish causality and to quantify how fibril composition and other factors influence scintigraphy performance.[8]

Positron emission tomography imaging with amyloid-binding radiotracers, such as 11C-Pittsburgh Compound B and 18F-labelled agents, holds promise for enhanced sensitivity in detecting cardiac amyloid deposits, including cases with negative bone scintigraphy and for differentiating between AL and ATTR amyloidosis.[15,16] Although PET scans are promising, their availability and high cost can restrict widespread clinical implementation. Therefore, clinicians should be aware of these limitations and consider a multimodality imaging approach combined with molecular diagnostics to optimize the accuracy of cardiac amyloidosis diagnosis, particularly in hereditary ATTR amyloidosis variants prone to false-negative scintigraphy results.

Timely identification of hereditary ATTR amyloidosis is of utmost importance, particularly in view of the availability of effective disease-modifying therapies. Pharmacologic agents such as tafamidis (a transthyretin stabilizer) and *TTR*-silencing therapies (e.g. RNA interference agents) have demonstrated significant efficacy in slowing disease progression and preserving functional status when initiated early. A prompt genetic and clinical diagnosis is therefore critical to reduce diagnostic inertia and prevent progressive and irreversible organ damage.[3,6,17,18]

Primary specialties involved other than cardiology

This case involved a multidisciplinary approach, with key contributions from gastroenterology, radiology, anatomical pathology, and genetics, in addition to cardiology.

Patient perspective

The patient and his family expressed relief at finally receiving a unifying diagnosis after a prolonged, frustrating diagnostic journey.

Lead author biography

Dr Lilaf Abdulmajid obtained her medical degree from the University of Antwerp, Belgium. She is currently training in cardiology at the University Hospital Antwerp and is completing her residency at Jessa Hospital in Hasselt, Belgium. Her clinical interests include heart failure and cardiac imaging.

Author contributions

Lilaf Abdulmajid (Writing—review & editing [lead]), Lucas Wauters (Writing—review & editing [supporting]), Tim Vanuytsel (Writing—review & editing [supporting]), Gert De Hertogh (Writing—review & editing [supporting]), Benjamin Peters (Writing—review & editing [supporting]), and Philippe Timmermans, Jr (Supervision [lead])

Acknowledgements

The authors thank the patient. This case report was presented by the first author at the ESC Heart Failure Congress (Clinical Case Award Session), where it was awarded first runner-up in the clinical case competition.

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient, in line with the COPE guidelines.

Conflict of interest: The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

Funding

No specific funding was received for this work.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this case report.

References

1. Poli L, Labella B, Cotti Piccinelli S, Caria F, Risi B, Damioli S, et al. Hereditary transthyretin amyloidosis: a comprehensive review with a focus on peripheral neuropathy. *Front Neurol* 2023;**14**:1242815.
2. Wixner J, Mundayat R, Karayal ON, Anan I, Karling P, Suhr OB, et al. THAOS: gastrointestinal manifestations of transthyretin amyloidosis—common complications of a rare disease. *Orphanet J Rare Dis* 2014;**9**:61.
3. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016.
4. Cipriani A, De Michieli L, Porcari A, Licchelli L, Sinigiani G, Tini G, et al. Low QRS voltages in cardiac amyloidosis: clinical correlates and prognostic value. *JACC CardioOncol* 2022;**4**:458–470.
5. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–3626.
6. Di Stefano V, Fava A, Gentile L, Guaraldi P, Leonardi L, Poli L, et al. Italian Real-life experience of patients with hereditary transthyretin amyloidosis treated with patisiran. *Pharmgenomics Pers Med* 2022;**15**:499–514.
7. Luigetti M, Romozzi M, Bisogni G, Cardellini D, Cavallaro T, Di Paolantonio A, et al. hATTR pathology: nerve biopsy results from Italian referral centers. *Brain Sci* 2020;**10**:780.
8. Musumeci MB, Cappelli F, Russo D, Tini G, Canepa M, Milandri A, et al. Low sensitivity of bone scintigraphy in detecting Phe64Leu mutation-related transthyretin cardiac amyloidosis. *JACC Cardiovasc Imaging* 2020;**13**:1314–1321.
9. Freudenthaler S, Hegenbart U, Schönland S, Behrens HM, Krüger S, Röcken C. Amyloid in biopsies of the gastrointestinal tract-a retrospective observational study on 542 patients. *Virchows Arch* 2016;**468**:569–577.
10. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic resonance in transthyretin cardiac amyloidosis. *J Am Coll Cardiol* 2017;**70**:466–477.
11. Lee SP, Park JB, Kim HK, Kim YJ, Grogan M, Sohn DW. Contemporary imaging diagnosis of cardiac amyloidosis. *J Cardiovasc Imaging* 2019;**27**:1–10.
12. Falk RH, Quarta CC, Dorbala S. How to image cardiac amyloidosis. *Circ Cardiovasc Imaging* 2014;**7**:552–562.
13. Saro R, Pavan D, Porcari A, Sinagra G, Mojoli M. Lights and shadows of clinical applications of cardiac scintigraphy with bone tracers in suspected amyloidosis. *J Clin Med* 2023;**12**:7605.
14. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016;**133**:2404–2412.
15. Khedraki R, Robinson AA, Jordan T, Grodin JL, Mohan RC. A review of current and evolving imaging techniques in cardiac amyloidosis. *Curr Treat Options Cardiovasc Med* 2023;**25**:43–63.
16. Li W, Uppal D, Wang YC, Xu X, Kokkinidis DG, Travin MI, et al. Nuclear imaging for the diagnosis of cardiac amyloidosis in 2021. *Diagnostics (Basel)* 2021;**11**:996.
17. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med* 2018;**379**:11–21.
18. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med* 2018;**379**:22–31.