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CASE REPORT
Heart failure

Beta 2-microglobulin: case report of a rare cause of cardiac amyloidosis

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Background Cardiac amyloidosis is caused by the deposition of misfolded proteins in the myocardium. The majority of cases of cardiac amyloidosis is caused by misfolded transthyretin or light chain proteins. In this case report, we discuss a case of a rare form of cardiac amyloidosis related to beta 2-microglobulin (B2M) in a patient not on dialysis.

Case summary A 63-year-old man was referred for workup of possible cardiac amyloidosis. Serum and urine immunofixation electrophoresis demonstrated no monoclonal bands, and the serum kappa/lambda light chain ratio was normal, excluding light chain amyloidosis. Bone scintigraphy imaging showed diffuse radiotracer uptake in the myocardium, and genetic testing of the *Transthyretin* gene was negative for variants. This workup was consistent with wild-type transthyretin cardiac amyloidosis. The patient, however, later underwent endomyocardial biopsy due to factors inconsistent with this diagnosis, including a young age of presentation and a strong family history of cardiac amyloidosis despite no variants in the *Transthyretin* gene. This showed B2M-type amyloidosis, and genetic testing of the B2M gene showed a heterozygous Pro32Leu (p. P52L) mutation. The patient underwent heart transplantation with normal graft function 2 years post transplant.

Discussion While contemporary advancements allow for the non-invasive diagnosis of transthyretin cardiac amyloidosis with positive bone scintigraphy and negative monoclonal protein screen, clinicians should be aware of rarer forms of amyloidosis where endomyocardial biopsy is required to make the diagnosis.

Keywords Cardiac amyloidosis • Beta 2-microglobulin • Case report

ESC Curriculum 2.5 Nuclear techniques • 2.1 Imaging modalities • 6.5 Cardiomyopathy

Learning points

- To have increased awareness of rare forms of cardiac amyloidosis.
- To acknowledge the limitations of technetium pyrophosphate imaging and the possibility of false positives in the case of light chain amyloidosis or other amyloidosis subtypes.

Introduction

Cardiac amyloidosis is caused by the deposition of misfolded proteins in the myocardium. The majority (>95%) of cases of cardiac amyloidosis is AL (light chain amyloidosis) or ATTR (transthyretin amyloidosis) subtype.[1] Current guidelines support the non-invasive workup of suspected cardiac amyloidosis through serum and urine immunofixation electrophoresis and serum-free light chains to evaluate for AL amyloidosis. If the monoclonal protein screen is negative, bone scintigraphy imaging can be performed with a positive result considered diagnostic of ATTR cardiac amyloidosis.[2] There are, however, a variety of other, rare forms of cardiac amyloidosis that can lead to false-positive bone scintigraphy imaging and may require endomyocardial biopsy for diagnosis in specific cases.

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Timeline

10 years prior to presentation	• Acute coronary syndrome with stent placed to left anterior descending artery
5 years prior to presentation	• Rotator cuff tear
Within a year prior to presentation	• Bilateral carpal tunnel syndrome • Development of dyspnoea on exertion and lower extremity oedema
June 2017	• Labs completed excluding light chain amyloidosis • Technetium pyrophosphate consistent with ATTR cardiac amyloidosis • Genetic testing of the *TTR* gene showed no mutation supporting a diagnosis of wild-type ATTR
2019	• Tafamidis was approved by the United States Food and Drug Administration and was prescribed to the patient; however, he was unable to afford the copay
2020	• Endomyocardial biopsy was performed for conclusive diagnosis and showed beta 2-microglobulin amyloidosis (AB2M) • Listed Status 6 for heart transplantation • Heart transplantation
2022	• Doing well with normal graft function 2 years post transplantation

Case presentation

The patient was a 63-year-old man who presented to the Cardiomyopathy Clinic with a 7-month history of dyspnoea on exertion and lower extremity oedema. The patient had a history of hypertension, dyslipidaemia, rotator cuff tear 5 years prior, bilateral carpal tunnel syndrome for which he had not undergone surgery, and coronary artery disease s/p left anterior descending artery percutaneous coronary intervention for acute coronary syndrome performed 10 years prior to presentation. Of note, the patient was of Portuguese descent with a family history of amyloidosis, although few details were available. His half-sister reportedly had cardiac amyloidosis diagnosed by endomyocardial biopsy, his half-brother had amyloidosis of an unspecified type, and his mother died at age 68 from reported heart failure, although the underlying aetiology was unknown.

On examination, pulse was 58 beats/min and blood pressure 102/70 mmHg. Jugular venous pressure was elevated at 10–12 cm water and he had a grade 2/6 systolic murmur. Electrocardiogram did not show low voltage; however, low voltage is not sensitive for amyloidosis diagnosis.[3]

Resting echocardiogram showed an ejection fraction of 60% with increased left ventricular wall thickness (left ventricular septum 1.5 cm and left ventricular posterior wall 1.5 cm). Left ventricular outflow tract obstruction was not assessed. Measurement of global longitudinal strain was not standardly performed at the time when the echocardiogram was completed, and thus, the presence of apical sparing could not be assessed.

Based on the echocardiogram, he was presumed to have hypertrophic cardiomyopathy vs. cardiac amyloidosis. Cardiac magnetic resonance imaging, however, demonstrated diffuse gadolinium uptake throughout the myocardium and diffusively elevated extracellular volume highly suggestive of ATTR amyloidosis.

Serum and urine immunofixation electrophoresis demonstrated no monoclonal bands, and the serum kappa/lambda light chain ratio was normal, excluding AL amyloidosis.[4] Technetium pyrophosphate scan showed diffuse uptake throughout the left ventricle; quantitative and semi-quantitative gradings were not performed as the study was done in 2017 prior to reporting standardization. Genetic testing demonstrated no *TTR* gene variants. Based on this evaluation, a diagnosis of wild-type ATTR amyloidosis was established.[3] Per ESC guidelines, tafamidis is typically the agent of choice in wild-type ATTR amyloidosis.[3]

Tafamidis is a protein stabilizer shown to significantly increase survival and lower the rate of decline in exercise capacity as measured by the 6 min walk test.[5] Gene silencing agents can also be considered in patients with variant ATTR amyloidosis and neuropathic disease, with or without cardiomyopathy.

However, the patient was unable to afford tafamidis due to a high copayment. Given progressive symptoms, he was evaluated for heart transplantation. A right heart catheterization was completed as part of the transplant evaluation with an endomyocardial biopsy for confirmation of the diagnosis given discrepancy between family history and lack of identified genetic variants. Congo red staining (*Figure 1*) showed apple-green birefringence on polarization microscopy. Mass spectrometry detected a peptide profile consistent with AB2M. Beta 2-microglobulin (B2M) serum level was measured post transplantation and was within normal range, more consistent with familial, rather than dialysis-related, B2M amyloidosis. Genetic testing of the *B2M* gene showed a variant of unknown significance, a heterozygous Pro32Leu (p. P52L) missense mutation. The PolyPhen-2 (polymorphism phenotyping v2)[6] is a tool which predicts the impact of amino acid substitutions on the structure and functioning of human proteins. This tool predicts that this mutation is 'probably damaging'. Given the determination that the variant was of unknown significance, cascade screening of family members was not performed, in line with guidelines.[7]

The patient had progressive heart failure symptoms warranting heart transplant evaluation. He was listed Status 6 and underwent transplantation 6 months later. The explanted heart showed AB2M amyloid deposition.

Discussion

Beta 2-microglobulin is a protein constituent of human leucocyte antigen Class 1. It is catabolized by the renal tubules and thus amyloidosis from B2M (AB2M) is most commonly observed in patients on chronic haemodialysis.[8] Post-mortem examination of individuals on long-term haemodialysis has demonstrated B2M amyloid deposits in organs throughout the body including the heart,[9] although the incidence has decreased with newer technologies to more effectively dialyze B2M.[10] Beta 2-microglobulin amyloidosis in patients on dialysis typically presents with osteoarticular symptoms including arthritis, arthropathy, progressive bone destruction, pathological bone fractures, carpal tunnel syndrome, and chronic synovitis. Visceral B2M involvement typically occurs later in the disease. Patients on haemodialysis who develop cardiac disease may manifest heart failure attributable to cardiac amyloid deposition with arrythmias and hypotension.[8]

There have been rare reports of AB2M in patients not on dialysis identified in non-cardiac tissues. A case report of a French family showed an autosomal dominant hereditary systemic amyloidosis due to an Asp76Asn (p. D96N) variant in the B2M gene. The disease manifested as gastrointestinal disease, autonomic neuropathy, and sicca syndrome. Post-mortem examination of one family member displayed AB2M deposits in the spleen, colon, liver, heart, salivary glands, and nerves.[11] There is also one case report of a family of Portuguese

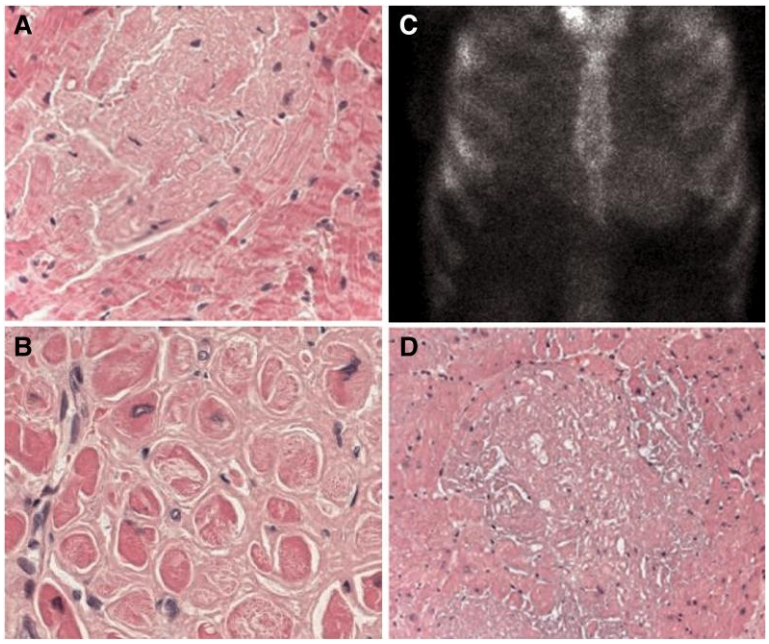

Figure 1 (*A*) Congo red stain of endomyocardial biopsy tissue. (*B*) High magnification—Congo red stain of endomyocardial biopsy tissue. (*C*) Anterior view of a scintigraphy scan showing cardiac radiotracer uptake. (Grading was not performed due to the study being completed prior to standardized reporting.) (*D*) Congo red stain of explanted heart tissue.

Table 1 Causes of false-positive and false-negative bone scintigraphy

	Notes	Useful references
Causes of false positives		
AL amyloidosis	The most common cause of false positives. It is critical to rule out AL amyloidosis through a negative monoclonal screen as AL-type amyloidosis requires immediate diagnosis and treatment	1–5
Amyloid apolipoprotein (A-I, A-II, and A-IV)	This rare amyloid subtype typically leads primarily to renal impairment but can also affect the heart	6
AB2M amyloidosis	This is usually seen in patients on long-term haemodialysis	6
Hypertrophic cardiomyopathy	Two patients with positive scintigraphy but upon workup with endomyocardial biopsy and genetic testing had myocyte hypertrophy and genetic variants. Another elderly gentleman with positive scintigraphy displayed sarcomeric hypertrophic cardiomyopathy	7, 8
Recent history of myocardial infarction	A patient with acute anterior non-ST-elevation myocardial infarction (NSTEMI) s/p percutaneous coronary intervention with stent placement to the left anterior descending artery 3.5 weeks prior. Bone scintigraphy showed an H/CL ratio of 1.6 and was read as Grade 3. Endomyocardial biopsy, however, was negative for amyloidosis. Analysis of single-photon emission computed tomography (SPECT) images showed that myocardial uptake was limited to the territory of the recent myocardial infarction	4
Hydroxychloroquine cardiac toxicity	Positive scintigraphy in a woman with a 15-year history of taking hydroxychloroquine for Sjogren's syndrome	9
Recent IV iron infusion	A patient with recent IV iron infusion for heart failure exacerbation had a positive scintigraphy scan. The scan was repeated 2 months later when he had received no iron infusion and was negative for amyloidosis	10
Planar imaging only performed	SPECT imaging should be completed to confirm myocardial uptake of the radiotracer. The blood pool in the ventricle or rib fractures can otherwise lead to false-positive planar imaging	11
Causes of false negatives		
Early disease	With minimal amyloid deposition scintigraphy may be negative or equivocal	11
Certain genetic variants	*TTR* variants—Ser77Tyr or Phe64Leu or Val30Met	6, 11

See Supplementary material online, *Appendix* for *Table 1* references.

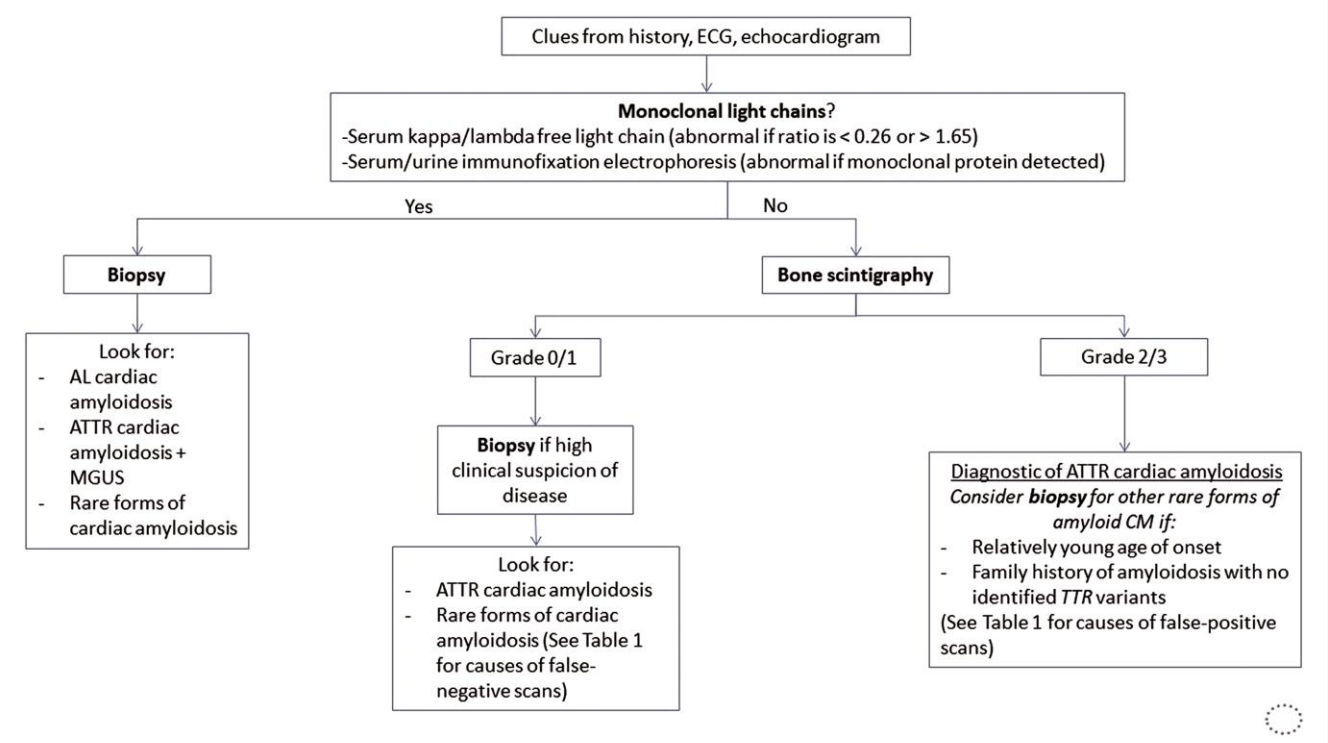

Figure 2 Decision tree for cardiac amyloidosis diagnosis. MGUS, monoclonal gammopathy of undetermined significance.

descent with the same mutation as this patient, a heterozygous variant Pro32Leu (p. P52L) in the *B2M* gene, resulting in symptomatic cardiac amyloidosis in three family members and requiring heart transplantation in one case.[12] Given that the family in our analysis was also of Portuguese descent, a common ancestor is possible. Although the variant is at this time categorized as a variant of uncertain significance, there are now two reports demonstrating pathogenicity of this variant.

The hereditary forms of the disease differ from dialysis-related AB2M amyloidosis in regard to the serum concentrations of B2M. In patients on dialysis with AB2M, amyloidosis the serum concentration of B2M is markedly increased. However, in hereditary AB2M amyloidosis serum B2M is mildly low or normal, and in the current case, the serum concentration of B2M was within normal limits.

Overall, over 95% of cases of cardiac amyloidosis are AL or ATTR subtype.[1] Non-invasive diagnosis is possible; a positive technetium pyrophosphate scan with a negative monoclonal protein screen is 99% accurate for the diagnosis, obviating the need for tissue biopsy in the majority of patients with ATTR cardiac amyloidosis.[1]

While this approach is beneficial in the diagnosis of cardiac amyloidosis, it is clearly not without limitations. False-negative bone scintigraphy scans can occur early in the course of disease or with specific *TTR* mutations[13] (Ser77Tyr or Phe64Leu or Val30Met) and an endomyocardial biopsy should be performed if there is a high clinical suspicion in the face of negative testing.

False-positive scans can also occur (see *Table 1*). Bone scintigraphy should never be interpreted in isolation; in ~10% of patients with AL amyloidosis, there is a false-positive bone scintigraphy scan[14] and if patients with AL amyloidosis are misdiagnosed with ATTR amyloidosis and not prescribed appropriate plasma cell-directed therapies, median survival can be less than a year.[15]

Although pyrophosphate imaging in the setting of negative AL lab workup shows high sensitivity and specificity for ATTR, this case report highlights a case of a false-positive pyrophosphate scan in the setting of AB2M-type amyloidosis. Other rare causes of cardiac amyloidosis such as amyloid apolipoprotein (A-I, A-II, and A-IV), immunoglobulin heavy chain, serum amyloid A, and gelsolin are also best diagnosed through endomyocardial biopsy with mass spectrometry analysis.[16] In this case, the delayed diagnosis of AB2M amyloidosis is unlikely to have affected the outcome. There are no approved treatments for AB2M amyloidosis, and treatment for ATTR amyloidosis with tafamidis was not started due to prohibitive cost. Management of heart failure for this patient would therefore have been the same/similar had the patient initially been diagnosed with AB2M amyloidosis.

In the current case, clinical clues to a rarer form of amyloidosis included a relatively young age (63) of onset for wild-type TTR amyloidosis and a family history suggestive of hereditary amyloidosis with no abnormality in the TTR gene. In such cases, endomyocardial biopsy should be considered to conclusively confirm the presence and subtype of amyloidosis (*Figure 2*).

Conclusion

Current guidelines support the use of serum and urine immunofixation electrophoresis and serum-free light chains to evaluate for AL amyloidosis and subsequent technetium pyrophosphate imaging to evaluate for ATTR amyloidosis if the monoclonal protein screen is negative. Despite the high sensitivity and specificity of bone scintigraphy in the diagnosis of ATTR amyloidosis, clinicians should be aware of the rarer forms that may be suggested by earlier age at presentation and/or a suspicious family history. With these clinical clues, endomyocardial biopsy may uncover a rarer form for which tafamidis is not indicated, family screening may be required, and prognosis may vary.

Lead author biography

Jack J. Haslett is a clinical research coordinator at Cedars-Sinai with an interest in heart failure, pulmonary hypertension, cardiac amyloidosis, and heart transplantation. Jack is dedicated to advancing medical knowledge and improving patient outcomes through his work.

Supplementary material

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

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The patient voluntarily agreed to participate in this case report and signed informed consent for publication per COPE guidelines.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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