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Present and future of endomyocardial biopsy in cardiac amyloidosis

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Cardiac amyloidosis (CA) affects the myocardium, vessels, valves, and epi-pericardium. Guidelines and expert consensus documents provide recommendations for the diagnostic work-up, which has the dual purpose of confirming the presence of amyloid deposits and characterizing the amyloidogenic protein. Amyloid typing is essential for treatments targeting the different types of amyloidosis, mainly transthyretin (ATTR, the most common type) and light chain, and less commonly reactive-serum amyloid-A, and beta2-microglobulin. Endomyocardial biopsy (EMB), still considered the gold standard for diagnosing and typing amyloid, is primarily reserved for cases where non-invasive tools do not provide a definitive diagnosis. Interestingly, while EMB was expected to decline, its numbers have increased globally over the past decade. This trend was driven by the greater awareness of CA, the novel epidemiology of CA with exponentially increased ATTRwt, the limitations of non-invasive methods in diagnosing early-stage ATTR CA, and the need to diagnose and type CAs that are not identified through alternative tools. Looking ahead, it is anticipated that EMB will continue to play a crucial role in diagnosing CA. This review explores the current diagnostic role of EMB, and potential applications in early CA, in differential diagnoses, in detecting and typing rare CA, as well as in incidental findings.

Introduction

Cardiac amyloidosis (CA) is a well-recognized heart disease and has now become an integral part of the clinical knowledge base of all cardiologists. While the suspicion of amyloidosis may arise in various specialized fields such as internal medicine, haematology, rheumatology, nephrology, and neurology, it is increasingly within the domain of cardiology that the initial diagnostic steps and subsequent in-depth evaluations are performed. Indeed, CA is a pan-heart disease, affecting myocardial tissue, valves, vessels, and the epi-pericardium, with clinical implications for cardiomyopathies, heart failure (HF)—particularly HF with preserved Ejection Fraction (HFpEF)—calcific aortic valve disease, coronary artery disease, and rhythm disorders.[1]

Of the 42 human amyloid fibril proteins recently acknowledged by the International Society of Amyloidosis Nomenclature Committee, 19 are associated with systemic deposition, with at least 9 potentially involving the heart.[2] Two forms of amyloidosis account for over 95% of CA cases: the ‘primary’, or light-chain amyloidosis (AL), and transthyretin amyloidosis (ATTR).[3] AL occurs when fibrils made of misfolded monoclonal immunoglobulin light chains infiltrate extracellular

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spaces in patients with clonal plasma cell proliferation.[4] ATTR CA may occur in patients carriers of amyloidogenic Transthyretin gene (*TTR*) variants (ATTRv) (1503/22886 6.6% patients referred for TTR gene testing)[5] or, far more commonly, when amyloid fibrils are formed from monomers/oligomers of the 'wild-type' tetrameric protein (ATTRwt). The prevalence is 12% in consecutive autopsy series and up to 37% in patients over 90.[6] Other, rarer forms of genetic amyloidosis that may involve the heart are caused by defects in *AApoAI* and *AApoAIV* genes.[2,7] In addition, the heart can be involved in secondary systemic amyloidosis,[2] such as beta-2 microglobulin (Aβ2 M) in dialysis patients, and reactive-serum amyloid-A (AA) amyloidosis, which can complicate chronic acquired and heritable autoinflammatory diseases (e.g. familial Mediterranean fever), lymphoproliferative disorders like Castleman's disease, and autoimmune diseases.

The diagnostic work-up for CA is well-defined by current guidelines[8] and expert consensus documents.[9] CA is suspected based on phenotypes, biomarkers, and imaging studies.[8] Diagnosis is confirmed through tissue biopsies, which demonstrate the extracellular amyloid deposition and allow precise identification of the amyloidogenic protein using light and electron microscopy immunohistochemistry[10,11] and mass spectrometry.[12] For many years, the gold standard for diagnosing CA was the endomyocardial biopsy (EMB). However, in systemic amyloidosis, where multiple organs or tissues are affected, extracardiac biopsies can obviate the need for EMB.[13] Moreover, in recent decades, ATTR CA diagnosis has increasingly been achieved non-invasively through bone scintigraphy (BS), particularly when myocardial radiotracer uptake is grade 2 or 3.[13] Therefore, given that tissue diagnosis can often be obtained through non-cardiac biopsies, and the majority of ATTR CA can be diagnosed non-invasively with BS, the role of EMB in the diagnostic workflow warrants re-evaluation. *This short review analyses the diagnostic insights provided by EMB, its current diagnostic role, and the potential future applications in both suspected CA cases and in screening studies.*

EMB-based diagnosis of cardiac amyloidosis

Historically, the pathological study of EMBs and whole affected hearts has been pivotal in advancing knowledge and precision diagnostic pathways for cardiac amyloidosis. The earliest pathological studies date back to the 1940s. Over the past 80 years, biopsy studies have progressively refined methods for tissue characterization of various amyloidogenic proteins. Today, tissue studies utilize not only advanced pathology techniques such as immuno-microscopy and immuno-electron microscopy but also mass spectrometry, which is considered the gold standard for amyloid characterization.[14]

EMB provides unique diagnostic information demonstrating extracellular amyloid infiltration, enabling specific labelling of antibodies targeting amyloidogenic fibrils, and providing myocardial samples for mass spectrometry, in particular in cases that remain uncharacterized by immunopathology or involve double amyloid components, e.g. AL and ATTR, or ATTR and AA.

While EMB carries inherent risks such as heart perforation and arrhythmias, these complications are rare (<1%), particularly in high-volume centres. *Greater collaboration between clinicians and pathologists is needed to facilitate the development of fast, on-site comprehensive diagnostic programmes, especially in tertiary cardiology centres.*

Increase of EMB despite 'apparently' reduced need

Paradoxically, the global burden of EMB has risen in the last decade, despite alternative diagnostic tools having become available. The increasing 'awareness' and the new epidemiology of CA—particularly ATTRwt—have driven the establishment of EMB-focused diagnostic programmes. For example, a nationwide pathology consultation programme in Japan was launched in 2018 following governmental approval of tafamidis and technetium scintigraphy for ATTR CA. From April 2018 to July 2022, of 5400 cases analysed, amyloid was typed in 4119 of 4420 Congo-red-positive cases. The incidence rates for AA, ALκ, ALλ, ATTR, Aβ2 M, and other forms were 3.2%, 11.3%, 28.3%, 54.9%, 0.6%, and 1.8%, respectively. Of 2208 EMBs, 1503 were ATTR positive.[15] An increased number of CA has been observed in a German nationwide study of 67 745 EMBs conducted between 2005 and 2019; the annual number of EMBs increased from 3083 in 2005 to 5646 in 2019. CA was diagnosed in 419/19 083 EMBs (2.2%) performed during 2005–2009. In subsequent five-year periods, the proportion of CA diagnoses further increased from 735/23095 (3.2%) EMBs in 2010–2014 to 1561/25795 EMBs (6.1%) in 2015–2019. Patients undergoing EMB in recent years were older and had more comorbidities, but complications were less frequent, highlighting the safety of the procedure.[16] The 'My Biopsy HF Study' (German Clinical Trials Register Number: DRKS22178), which retrospectively analysed 655 patients with unexplained HF, found incidental CA in 38 patients (5.8%). Among these, 15 patients (2.3%) were diagnosed with AL CA and 23 patients (3.5%) with ATTR CA (17 ATTRwt and 6 ATTRv). A multivariate logistic regression analysis adjusting for age, sex, and comorbidities revealed that only CA, advanced age, and New York Heart Association (NYHA) functional class III/IV were independently associated with all-cause mortality over a median follow-up of 4.6 years.[17] The overall rising awareness of CA and the higher detection rate of ATTRwt CA in elderly patients have positioned EMB as a potential screening tool for patients with an HFpEF phenotype[18] or in patients with hypertension, left ventricular hypertrophy (LVH), and heart failure of unclear/unknown aetiology.[19]

EMB in clinically suspected CA and guidelines

Although most manuscripts/review articles reiterate that the gold standard for the diagnosis of CA is EMB, guidelines recommend EMB as a Class IIa procedure with a Level of Evidence C.[8,9] According to the 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With CA, '*EMB should be performed (if other tissue biopsy does not*

confirm amyloid) in the following scenarios: (1) high clinical suspicion of CA in a patient with a monoclonal protein by immunofixation electrophoresis and/or an abnormal sFLC K/L ratio above the upper range of normal; (2) high clinical suspicion for cardiac amyloidosis despite negative or equivocal Tc-PYP imaging; or (3) cardiac scintigraphy is unavailable'.[9] Guidelines do not include recommendations for AA CA or Aβ2 M CA or other rare CA.

Generally, patients with suspected CA should first undergo monoclonal protein screening; when serum and urine immunofixation electrophoresis exclude monoclonal bands, and the serum kappa/lambda light chain ratio is normal, AL amyloidosis is excluded. These tests provide the basis for further diagnostic steps, either towards confirming AL CA or exploring other forms of CA, particularly ATTR CA.[8,9] For patients with suspected ATTR CA, tissue biopsy—specifically EMB—is not required when myocardial radiotracer uptake is grade 2 or 3. Additionally, in patients with any pre-existing biopsy-positive sample from non-cardiac sites, the amyloid typing can be achieved without further biopsies, potentially obviating the need for EMB. However, if the amyloid type identified in a non-cardiac biopsy is inconsistent with the patient's clinical presentation, EMB may be necessary for CA typing.

While guidelines aim '*to assist healthcare professionals in recommending the best diagnostic or therapeutic approaches for individual patients*',[8] considerable flexibility remains for clinicians. *This allows personalization of diagnostic work-up, including EMB, based on the clinical scenarios and health conditions of each patient.*

Clinically guided scenarios for EMB

The following paragraph summarizes the clinical scenarios in which EMB is necessary to provide a certain diagnosis of CA and type the amyloidogenic protein/s.

(1) Patients with suspected ATTR CA and BS score of 0 or 1.
EMB may be necessary to confirm or exclude ATTR CA in patients with clinical criteria suggesting CA but a negative or ambiguous/uncertain BS radiotracer uptake (scores 0 and 1). Indeed, patients with biopsy-confirmed CA may show no cardiac uptake of the radiotracer on BS. For instance, in a series of 271 patients, 14 (5%) had negative BS, with four of seven retested patients later showing positive BS. Ultimately, 6 of the 14 biopsy-confirmed ATTR-CM patients had no cardiac radiotracer uptake.[20]

(2) Genetic testing positive and BS negative
Patients with clinical traits and biomarkers suggestive of CA, who test positive for amyloidogenic *TTR* gene variants but show negative or ambiguous BS (scores 0 and 1), may require EMB to confirm or rule out the presence of CA (*Figure 1*, panel A).

(3) Patients with positive BS (Scores 2 or 3) and monoclonal gammopathy of unknown significance (MGUS)
MGUS, common in ATTR amyloidosis, may complicate diagnosis. EMB can confirm the presence of dual amyloid fibrils or exclude AL CA. AL amyloidosis was diagnosed in 3 of 31 patients (10%) with monoclonal proteins and a BS score ≥2.[21]

(4) Suspected AL CA Requiring Urgent Treatment
In patients clinically requiring prompt diagnosis, EMB can be rapidly performed and processed to expedite treatment. 'Fast-track' processing (6 hours) of EMB samples provides the immediate diagnosis of CA (CA yes or not). Full processing for amyloid typing using both light and electron immunostains takes up to 4 days. Occasionally, rapid decisions need to be made in CA-suspected critically ill patients with positive monoclonal protein screening (e.g. acute HF with reduced EF in unreported patients, or iatrogenic —e.g. bortezomib—cardiogenic shock)

(5) Monoclonal Gammopathy and light chain deposition disease (LCDD)
LCDD affecting the heart may mimic CA, but Congo Red stains negative and electron microscopy excludes the presence of amyloid fibrils. Although LCDD most commonly involve kidneys, the diagnosis can be missed. In these cases, EMB provides the diagnosis, which is essential for treatment.[22]

(6) Autoimmune or chronic inflammatory diseases
Patients with long-standing inflammatory diseases may develop cardiac phenotypes wit diastolic dysfunction similar to restrictive cardiomyopathy. EMB can confirm the presence of AA CA.[23]

(7) Heritable Autoinflammatory Disorders
Patients with autoinflammatory diseases (e.g. familial Mediterranean fever), typically presenting with kidney involvement, may develop systemic AA that can affect the heart. In these cases, EMB is the key diagnostic tool.[23]

(8) Lymphoproliferative disorders
Patients with rare lymphoproliferative disorders such as Castelman's disease may manifest cardiac traits suggestive of cardiomyopathy: EMB can demonstrate AA CA, which may reverse after resolution of the primary cause.[24]

(9) Aβ2 M CA: Dialysis-related systemic amyloidosis and genetic Aβ2M
Patients with chronic kidney disease may develop systemic dialysis-related amyloidosis (DRA) resulting from the kidneys' impaired ability to degrade β_2-microglobulin (β_2m). The heart involvement is rare, but should be considered as possible in these patients.[25] In addition to DRA, the rare possibility that Aβ2 M CA occur in patients carrying defects of *B2 M* gene must be considered (https://omim.org/entry/620659).

Future clinical scenarios and EMB

The use of EMB is expected to expand in various clinical scenarios, including the following:

(1) **Early Diagnosis in familial ATTRv amyloidosis.**
Genetic-positive relatives of patients carrying amyloidogenic TTR gene variants could benefit from early EMB-based diagnoses.[8] Early treatment for ATTR CA has the potential to improve the disease's natural course and prognosis. EMB might increasingly be applied in carriers of amyloidogenic *TTR* variant with clinically suspected CA with BS scores 0 or 1,

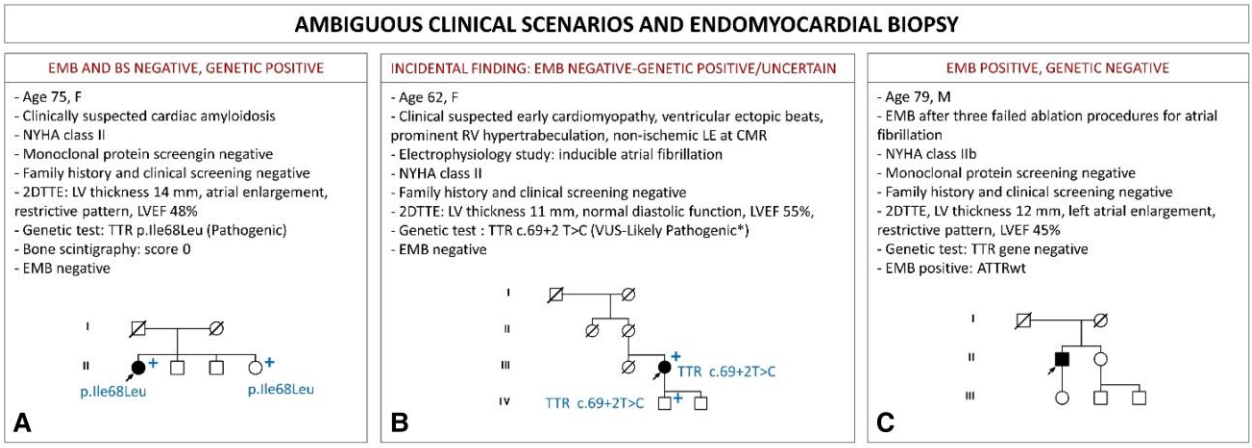

Figure 1 *Figure 1* illustrates three distinct ambiguous clinical scenarios where endomyocardial biopsy (EMB) provided a definitive diagnosis. Panel *A*) describes a 72-year-old woman with clinical suspicion of cardiac amyloidosis. Despite carrying a pathogenic *TTR* gene variant, bone scintigraphy was negative and endomyocardial biopsy confirmed the absence of amyloid deposits in the heart. Her sister, who carriers the same genetic variants, showed normal morphofunctional cardiac profile. Panel *B*) features a genetic incidental finding in a biopsy-negative case. The patient is a 65-year-old woman with suspected early, non-otherwise specified, cardiomyopathy. The multigene panel sequencing identified the c.69 + 2T > C variant affecting a canonical splicing site of the *TTR* gene. Although these types of variants may fulfil the ACMG criteria of pathogenicity (PVS1 criterion for protein loss-of-function effect and PM2 for the extremely low frequency in population databases), most amyloidogenic variants are missense, causing protein misfolding rather than loss of function. For this reason, we classified the c.69 + 2T > C as non-amyloidogenic variant of uncertain significance (VUS). Endomyocardial biopsy confirmed the absence of amyloid in the heart. Panel *C*) describes a 79-year-old man with recurrent atrial fibrillation after multiple ablations and atrial enlargement (case referred to our attention in 2012). In this patient, the EMB confirmed ATTR cardiac amyloidosis and the *TTR* gene tested negative. EMB, endomyocardial biopsy; F, female; M, male; NYHA, New York Heart Association; RV, right ventricular; LE, late gadolinium enhancement; CMR, cardiac magnetic resonance; 2DTTE, two dimensional transthoracic echocardiography; LV, left venticular; LVEF, left ventricular ejection fraction; VUS, variant of uncertain significance.

where precise diagnosis cannot be achieved through non-myocardial tissue analysis.

(2) **Heart Failure of Unknown Aetiology.**

In heart failure—especially HFpEF and HF with mildly reduced EF—of unknown origin, screening programmes could eventually include EMB.[17–19] For elderly patients with ATTRwt CA, where heart failure is often the primary determinant of prognosis despite comorbidities, EMB screening has already proven relatively straightforward and safe, with a detection rate for CA of up to 10%. Moderate or severe interstitial ATTRwt deposition was present in 5/109 (5%) patients (80% men), with mild interstitial and/or variable severity of intramural coronary vascular deposition in 13 (12%) patients.[26]

(3) **Systemic Iatrogenic Amyloidosis.**

Emerging cases of systemic iatrogenic amyloidosis linked to injectable protein drugs (e.g. anakinra) have been reported. This form of amyloidosis, known to affect the skin, gastrointestinal tract, and kidneys, represents a novel area for investigation. Cardiologists may be called upon to monitor the cardiac function of young patients undergoing chronic treatment with anti-IL-1 agents[27] and eventually explore the heart involvement in patients with instrumental abnormalities or symptoms.

(4) **Incidental detection of amyloidosis in non-cardiac tissue samples**

Retrospective studies have revealed an increasing rate of ATTRwt amyloidosis detection in urinary tract and prostate biopsy series. In a large series of Congo-red-positive prostatic and urinary tract samples, Gilani and Coll. found ATTR amyloidosis in 37% of urinary tract (286/767, 37%) and 37% (55/150, 37%) of prostatic samples. Of 48 pts in whom 'the urinary tract/prostate was the site of the initial ATTR amyloidosis diagnosis', 38/48 (79%) were subsequently diagnosed with CA.[28] This entails a practical consideration for cardiologists, e.g. cardiac 'red flags' of CA, when evaluating patients with urinary tract/prostatic diseases before surgery.

(5) **Incidental (or secondary) Findings in Genetic Testing**

EMB could play a critical role in patients undergoing expanded genetic testing (multigene panels, whole exome sequencing), which reveals incidental pathogenic variants in *TTR* gene, which is listed in the American College of Medical Genetics and Genomics (ACMG) guidelines for reporting secondary findings (https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/). While these patients will undergo comprehensive non-invasive cardiac evaluations, EMB may remain the only definitive test for eventually diagnosing CA (*Figure 1*, panel B).

(6) **Arrhythmias.** EMB may play a role in managing recurrent arrhythmias, particularly atrial fibrillation resistant to multiple ablations (*Figure 1*, panel C). Further research is needed to define its application in rhythm disorders.

(7) **Calcific Aortic Valve Disease**

Distinguishing calcific aortic valvulopathies in elderly patients with ATTRwt CA from those without CA remains matter of active research. In ATTRwt CA, amyloid deposits are frequently found in cardiac valves, whereas in non-CA cases, the role of

amyloid detected in aortic valves (Congo-red and Immuno-histochemistry) is debated and deserves further investigation.

(8) **Coexisting ATTRwt CA in patients with coronary artery disease (CAD): Coronary Amyloidosis**

Emerging clinical observations highlight the possibility that ATTRwt CA co-occur in patients with CAD. Indeed, out of 114 confirmed CA patients, 28 (25%) had concomitant CAD and CA.[29] The pioneering case described by Yoshida and Coll. anticipates the possibility that in case of certain coexistence of ATTR CA (documented with EMB and BS) and CAD, a directional coronary atherectomy (DCA) can be used to debulk the coronary lesion and assess the presence of amyloid in the coronary artery. DCA samples in fact enabled histologic diagnosis of coronary amyloidosis.[30]

Conclusions

EMB is more relevant and expanding as a diagnostic tool today than ever before. While it may appear overshadowed by the rise of non-invasive diagnostic methods primarily focused on detecting the more prevalent ATTR CA, the growing understanding of disease mechanisms—including secondary forms of CA, genetic non-TTR CA, and the extensive involvement of various cardiac structures (myocardial tissue, valves, vessels, and epicardium)—underscores EMB's future significance. It is poised to play a unique role in delivering precise diagnoses, guiding treatment strategies, and serving as a potential tool for monitoring therapeutic effectiveness.

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Data availability

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