ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Supporting Role of Adequate Affected Tissue Biopsy in the Diagnostic Algorithm for Cardiac Amyloidosis

Kardiyak Amiloidoz Tanısal Algoritmasında Yeterli Etkilenen Doku Biyopsisinin Destekleyici Rolü

ABSTRACT

Amyloidosis is a pathology that occurs as a result of the accumulation of various misfolded proteins in the extracellular space. It is a significant cause of morbidity and mortality due to multi-organ involvement. One of the most important determinants of mortality and morbidity is cardiac involvement. Cardiac amyloidosis (CA) may present with a variety of clinical findings. In this article, we aim to demonstrate the supportive role of cardiac and extra-cardiac tissue in the routine diagnostic pathway for CA.

Keywords: Amyloidosis, cardiomyopathy, heart failure

ÖZET

Amiloidoz, yanlış katlanmış çeşitli proteinlerin hücre dışı boşlukta birikmesi sonucu ortaya çıkan bir patolojidir. Çoklu organ tutulumu nedeniyle ciddi bir morbidite ve mortalite nedenidir. Mortalite ve morbiditenin en önemli belirleyicilerinden biri kardiyak tutulumdur. Kardiyak amiloidoz (KA) çok sayıda klinik bulgu ile karşımıza çıkabilir. Bu yazıda kardiyak ve kalp dışı doku biyopsisinin rutin tanı yolundaki destekleyici rolünü göstermeyi amaçladık.

Anahtar Kelimeler: Amiloidoz, kardiyomiyopati, kalp yetmezliği

CASE REPORT
OLGU SUNUMU

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Received: July 28, 2022
Accepted: June 28, 2023

Cite this article as: Bulut Bingöl G, Tok Ö, Özmen E, Avcı Demir F, Ökçün B. Supporting role of adequate affected tissue biopsy in the diagnostic algorithm for cardiac amyloidosis. *Turk Kardiyol Dern Ars.* 2024;52(2):143-148.

DOI:10.5543/tkda.2023.92265

We present the diagnostic processes for cardiac amyloidosis cases, illustrated through three distinct clinical scenarios, each diagnosed via biopsy samples from varied regions at our center.

Case 1

A 76-year-old male patient presented with difficulty in swallowing and swelling in the legs, which started two months ago and gradually worsened. Previously, the patient was examined at an external center with a preliminary diagnosis of amyotrophic lateral sclerosis for the same symptoms, but no conclusive results were obtained after many diagnostic tests. During hospitalization for aspiration pneumonia at an external center, transthoracic echocardiography (TTE) was performed and found to be unremarkable.

The patient has a history of hypertension (HT), diabetes mellitus (DM), and a 50 pack-year smoking habit. On admission, his physical examination revealed a blood pressure (BP) of 95/55 mmHg, heart rate of 67 bpm, an apical 2/6 systolic murmur, and decreased bilateral lung sounds in the basal zones. Bilateral ++/++ pretibial edema was observed. His electrocardiography (ECG) showed a normal sinus rhythm, heart rate of 72 bpm with left axis deviation, and low QRS voltage in all derivations. The patient had hypoalbuminemia, and elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (18,463 pg/mL, N: < 486 pg/mL) and troponin T levels (0.221 ng/mL, N: < 0.014), and was hospitalized for further examination and treatment.

In the TTE, left ventricular (LV) systolic functions were normal, but right ventricular (RV) systolic functions were decreased. Significant LV concentric hypertrophy [interventricular septum (IVS): 18 mm, posterior wall (PW): 17 mm], left atrial (LA) enlargement, mild mitral regurgitation (MR), and minimal pericardial effusion were observed. The estimated pulmonary artery systolic pressure (sPAP) was 47 mmHg. Strain

analysis could not be performed because the echo machine that was used lacked this feature. A gastroenterology consultation was requested due to the patient's progressive dysphagia. As his echocardiography showed left ventricular hypertrophy, which was not observed previously, and his Electrocardiogram (ECG) revealed low voltage QRS, amyloidosis was suspected. For the diagnosis of amyloidosis, ^{99m}Tc-pyrophosphate (PYP) scintigraphy was planned. However, due to a temporary technical problem with the scintigraphy device, ^{99m}Tc-PYP scintigraphy could not initially be performed. Cardiac magnetic resonance imaging (CMRI) revealed a mild decrease in LV systolic functions [Left Ventricular Ejection Fraction (LVEF) 50%], biatrial enlargement, and diffuse LV thickening with no late gadolinium enhancement (LGE). CMRI findings were significant for restrictive cardiomyopathy. A bone marrow biopsy was performed at hematology's request, and the results showed nothing that would point to amyloidosis.

Subsequently, a ^{99m}Tc-PYP scintigraphy was conducted, detecting grade 3 cardiac involvement (Figure 1), and as a result, Transthyretin (TTR) type amyloidosis diagnosis was considered. During follow-up, the patient suffered from progressive dysphagia, and an upper gastrointestinal system endoscopy was carried out. Immunohistochemical examination of the biopsy taken from the esophageal narrowing area showed subepithelial amyloid accumulation in the esophagus and diffuse, massive amyloid accumulation in the superficial submucosal area of the antrum (Figure 2). Subtype analysis could not be performed. Transthyretin (TTR) gene analysis was negative for TTR mutation. The patient with significant involvement in ^{99m}Tc-PYP scintigraphy, absence of plasma cell dyscrasia in the bone marrow biopsy, and no TTR gene mutation was diagnosed with senile amyloidosis. Three months after the diagnosis, the patient died due to sudden cardiac death during his hospitalization at our center. In this case, esophageal biopsy did not have an absolute indication according to guideline recommendations, but due to progressive dysphagia, an endoscopy and esophageal biopsy were performed, which confirmed the already noninvasively diagnosed amyloidosis.

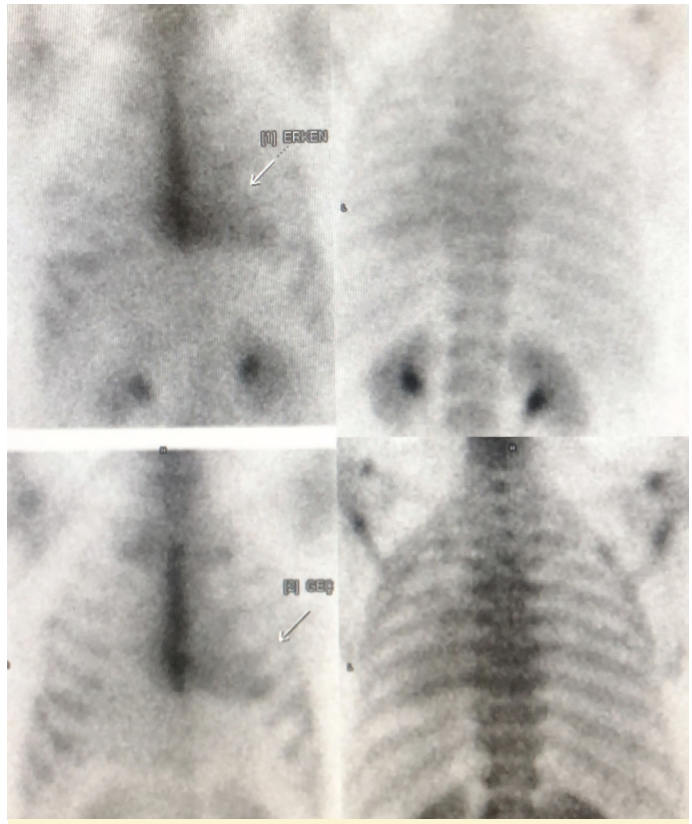

Figure 1. Grade 3 cardiac involvement observed in pyrophosphate scintigraphy.

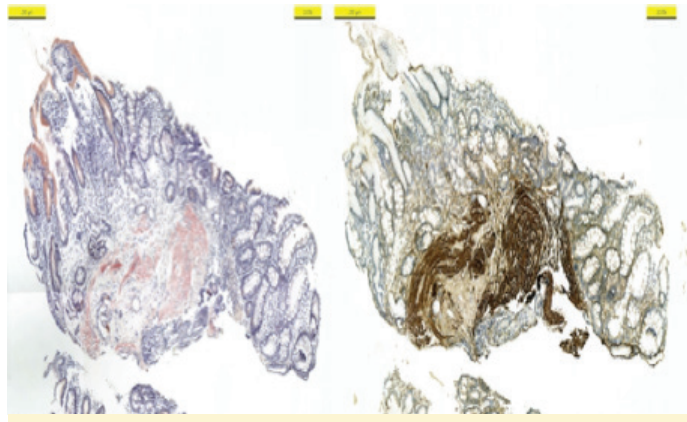

Figure 2. Gastric and esophageal biopsy showing accumulation of amyloid with amyloid P and Congo red staining.

ABBREVIATIONS

AL	Amyloid light chain
BNP	Brain natriuretic peptide
BP	Blood pressure
CMRI	Cardiac magnetic resonance imaging
CMV	Cytomegalovirus
DM	Diabetes mellitus
ECG	Electrocardiography
EMB	Endomyocardial biopsy
HL	Hyperlipidemia
HT	Hypertension
IAS	Interatrial septum
IVS	Interventricular septum
LA	Left atrium
LGE	Late gadolinium enhancement
LV	Left ventricle
LVEF	Left ventricle ejection fraction
MGUS	Monoclonal gammopathy of undetermined significance
MR	Mitral regurgitation
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PW	Posterior wall
PYP	Pyrophosphate
sFLC	Serum free light chain
sPAP	Systolic pulmonary artery pressure
TTE	Transthoracic echocardiography
TTR	Transthyretin

Case 2

A 63-year-old male with a history of HT and DM for 15 years presented to our clinic with complaints of weakness, fatigue, and sweating starting six years ago. On physical examination, the BP was 124/76 mmHg, and the heart rate was 86 bpm. Cardiac examination revealed that the apical beat was shifted to the left but no other abnormalities were detected. The ECG showed a sinus rhythm with low QRS voltage in all derivations. Laboratory

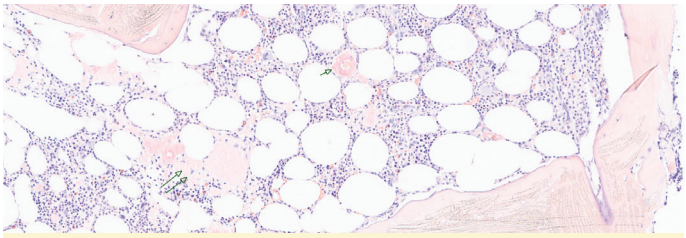

Figure 3. Congo red staining reveals material accumulation that appears positive in the bone marrow (single arrow indicates periareolar deposition; double arrow indicates interstitial substance deposition), (Congo-red, x100).

results showed no pathology except mild brain natriuretic peptide (BNP) elevation (548 pg/mL) and a mild increase in troponin levels. TTE revealed a LVEF of 60%, hypertrophy of the LV (IVS: 14 mm), and dilation of the LA. In ^{99m}Tc-PYP scintigraphy performed for suspected cardiac amyloidosis, grade 2 cardiac involvement was observed. Serum/urine protein electrophoresis, serum/urine immunofixation electrophoresis, and serum free light-chain analysis indicated a monoclonal plasma cell disorder. Subsequently, he underwent a bone marrow biopsy, which revealed vascular and interstitial involvement with amyloidosis and 4% polyclonal plasma cell infiltration. The patient had significant proteinuria in the 24-hour urinalysis. Due to predominant renal involvement, a renal biopsy was conducted and it revealed non-Amyloid A (non-AA) amyloidosis. The patient was referred to hematology department. No monoclonal plasma cell disorder was detected by serum/urine protein electrophoresis, serum/urine immunofixation electrophoresis, and serum free light-chain analysis. His bone marrow biopsy revealed vascular and interstitial involvement with amyloidosis and 4% polyclonal plasma cell infiltration. A subtype analysis of the renal biopsy materials was compatible with Amyloid Light-chain (AL) amyloidosis (Figure 3).

After the diagnosis of AL amyloidosis, chemotherapy and an autologous bone marrow transplantation were planned. During the follow-up, the patient developed atrial fibrillation and was treated with enoxaparin. While receiving chemotherapy, chemotherapy, he developed Cytomegalovirus (CMV) pneumonia and gastrointestinal system bleeding, and unfortunately died six months after the diagnosis.

Case 3

A 62-year-old female patient with known diagnoses of HT and hyperlipidemia (HL) presented to our clinic with complaints of shortness of breath, nausea, vomiting, and fatigue. Her complaints, especially dyspnea, had gradually worsened over the last year.

TTE performed at the onset of the patient's complaints revealed only mild LV hypertrophy and mild LA enlargement. Laboratory tests were unremarkable. During the physical examination, BP was 89/56 mmHg and heart rate was 64 bpm. An apical 3/6 systolic murmur was heard, lung sounds were decreased in the basal zones without rales, and bilateral pretibial edema, jugular venous distension, and abdominal examination findings consistent with ascites were also noted.

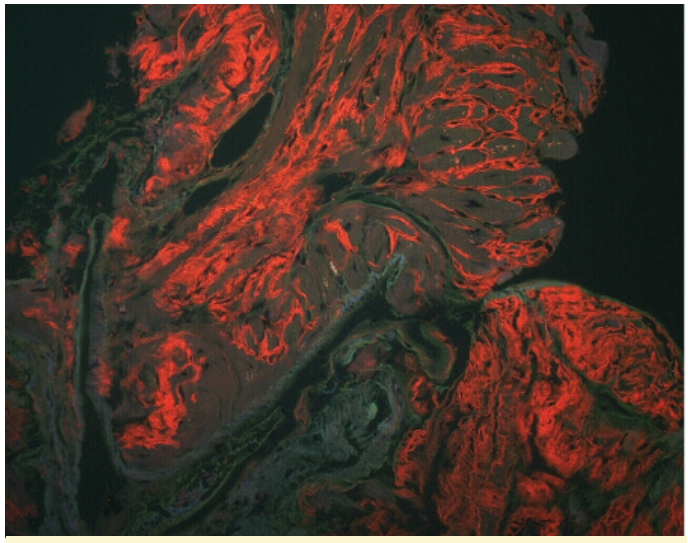

Figure 4. Myocardial biopsy material from the patient 2. Congo Red-positive protein accumulation is observed.

Her ECG showed sinus rhythm with low voltage and rare ventricular premature beats. Laboratory findings included creatinine at 1.67 mg/dL, BNP at 1,629 pg/mL, and troponin T at 255 ng/mL (0-15). TTE revealed a LVEF of 40% with global hypokinesia, LV hypertrophy [IVS: 13 mm, Posterior Wall thickness at end-diastole (PWd): 14 mm], biatrial enlargement, and moderate MR. Estimated sPAP was 50 mmHg. Right heart chamber dimensions and right ventricle systolic function parameters were within normal limits. Given the patient's left ventricular dysfunction and high pulmonary artery systolic pressure on echocardiography, coronary angiography and right heart catheterization were planned to exclude restrictive cardiomyopathy. Coronary angiography revealed normal coronary arteries. Right heart catheterization results were as follows: pulmonary artery mean pressure: 18 mmHg, pulmonary capillary wedge pressure: 25 mmHg, pulmonary vascular resistance: 2.1 Wood units. ^{99m}Tc-PYP scintigraphy could not be performed due to technical issues.

CMRI findings included global hypokinesia of the LV with an LVEF of 40%, ventricular and interatrial septum (IAS) thickening, subendocardial-midmyocardial late gadolinium enhancement, and a suspected diagnosis of amyloidosis. Serum immunofixation electrophoresis demonstrated lambda light chain monoclonal gammopathy. Consequently, a rectal biopsy was planned, but no findings compatible with amyloidosis were found in the biopsy results. During follow-up, the patient exhibited progressive dyspnea and orthostatic hypotension. After discussing with hematologists, an endomyocardial biopsy (EMB) was planned due to its high sensitivity and specificity, and because EMB can be performed at our center with subtype analysis of the biopsy materials. The EMB result was compatible with AL amyloidosis. Protein deposits that stained positive with Congo red and showed green fluorescence were found in 30% of the tissue (Figure 4). Protein accumulation was observed in the interstitial area, and Fabry Disease was excluded due to the absence of intracellular accumulation. While the patient was being managed in the hospital for heart failure, she unfortunately died due to decompensated heart failure.

Table 1. Clinical Characteristics of the Patients

	Case 1	Case 2	Case 3
Age (years)	76	63	62
Gender	Male	Male	Female
Admission Symptom	Difficulty in swallowing, pedal edema	Fatigue	Dyspnea
Symptom Duration	2 months	6 years	1 year
NYHA Class	III	II-III	III
Body Mass Index	20 kg/m^2	33 kg/m^2	22 kg/m^2
Physical Examination	BP: 95/55 mmHg Apical 2/6 systolic murmur Bilateral decreased lung sounds Pretibial edema	BP: 124/76 mmHg Apical beat shifted to left	BP: 89/56 mmHg Apical 3/6 systolic murmur Basal lung sounds decreased
ECG Findings	Sinus rhythm Low QRS voltage Left axis	Sinus rhythm Low QRS voltage	Sinus rhythm Low QRS voltage
Laboratory tests	ProBNP: 18,463 pg/mL Troponin T: 0.221 ng/mL	BNP: 548 pg/mL Troponin T: 118 ng/mL	Cre: 1.67 mg/dL BNP: 1,629 pg/mL Troponin T: 255 ng/mL
TTE Findings	LVEF 55% IVS: 18 mm, PWd: 17 mm LA dilated Mild MR PAPs: 47 mmHg Mild pericardial effusion Decreased right ventricular systolic function	LVEF 60% IVS: 14 mm LA dilated	LVEF 40% Global hypokinesia IVS: 13 mm, PWd: 14 mm Biatrial dilatation Moderate MR Estimated PAPs: 50 mmHg
Cardiac Involvement in 99mTc-PYP Scintigraphy	Grade 3	Grade 2	-
CMRI Findings	LVEF 50% Biatrial dilatation No LGE	-	LVEF 40% Ventricular and IAS thickening Subendocardial and midmyocardial LGE
Biopsy Findings	Esophagus biopsy: Amyloidosis	Renal biopsy: Consistent with amyloidosis Bone marrow biopsy: Consistent with AL amyloidosis	Rectal biopsy: No significant finding Myocardial biopsy: Consistent with AL amyloidosis
Genetic Mutation Test	TTR mutation negative	-	-
Final Diagnosis	Senile amyloidosis	AL amyloidosis	AL amyloidosis

AL, Amyloidosis Light Chain; BNP, Brain Natriuretic Peptide; BP, Blood Pressure; CMRI, Cardiac Magnetic Resonance Imaging; Cre, Creatinine; ECG, Electrocardiogram; IVS, Interventricular Septum; LA, Left Atrium; LGE, Late Gadolinium Enhancement; LVEF, Left Ventricular Ejection Fraction; MR, Mitral Regurgitation; NYHA, New York Heart Association; PAPs, Systolic Pulmonary Artery Pressure; PWd, Posterior Wall Diameter; TTE, Transthoracic Echocardiography; TTR, Transthyretin.

Discussion

Cardiac amyloidosis is a pathological condition of the heart caused by the accumulation of misfolded proteins in the extracellular space.[1]

Diagnosis of cardiac amyloidosis is often delayed as it is a rare disease with different non-specific clinical presentations. However, early diagnosis and specific treatment based on the type of amyloid are associated with a better prognosis and reduced mortality. Recently, thanks to greater clinical awareness and the advancement of modern non-invasive diagnostic methods, there has been increasing interest in the identification of cardiac amyloidosis. Although histopathological examination, which reveals amorphous deposits of amyloid fibrils, remains the gold standard for diagnosis among all methods,[2] the latest guidelines support the use of noninvasive methods for its diagnosis.

Today, more than thirty proteins have been identified that can accumulate as amyloid, and nine of these are known to cause cardiac amyloidosis.[3] Two of these proteins, monoclonal immunoglobulin light chains (AL) and transthyretin (ATTR), are known to be the cause of the vast majority of cardiac amyloidosis cases. ATTR amyloidosis can be acquired or hereditary due to mutations in the TTR gene.[4] Cardiac involvement, which is common in AL amyloidosis, is an important prognostic indicator. The prognosis of AL amyloidosis is poor in the presence of cardiac involvement.

The symptoms seen in patients with cardiac amyloidosis arise from right and left heart failure and may present with various clinical manifestations. Suspicious findings in patients' symptoms are defined as red flags (List 1).[1,5]

The diagnostic tests for cardiac amyloidosis can include laboratory tests, ECG, TTE, CMRI, radionuclide bone scintigraphy, genetic analysis, and tissue biopsies. The diagnostic process starts with clinical history, physical examination, ECG, and transthoracic echocardiography.[6] TTE typically shows concentric LV wall thickening accompanied by right ventricular involvement.[1] One of the best-defined findings is the discordance between QRS voltage and left ventricular wall thickness; low voltage is seen in 30% of cases, but its absence does not exclude the diagnosis.[7]

As expected, ECG hypovoltage and varying degrees of LV wall thickening on TTE were observed in all our three cases.

TTE generally shows concentric LV wall thickening (typically greater than 12 mm), which is accompanied by atrioventricular valve thickening, right ventricle free wall, interatrial septum thickening, biatrial enlargement, diastolic dysfunction, and reduced longitudinal strain with an apical sparing pattern.[1]

CMRI is an emerging tool for the detection of cardiac amyloidosis. Patients with cardiac amyloidosis show various characteristic LGE patterns in CMRI, which can provide important information about myocardial tissue and its content and help differentiate it from other cardiomyopathies that cause increased left ventricular wall thickness. These patterns include global subendocardial LGE, global transmural LGE, atrial LGE, and suboptimal myocardial T1-nulling. CMRI is very useful for excluding amyloidosis in suspected cases; however, it is important to note that CMRI alone is not sufficient for the diagnosis of cardiac amyloidosis. Furthermore, it cannot distinguish between Amyloid Light-chain Cardiomyopathy (AL-CM) and Transthyretin Cardiomyopathy (ATTR-CM).[8]

^{99m}Tc-labeled scintigraphy is a method with high sensitivity and specificity in the diagnosis of ATTR-type amyloidosis. Although there are different agents for ^{99m}Tc scintigraphy, the most frequently used and recommended one is PYP. PYP is significantly retained in the heart infiltrated with TTR, unlike the heart tissue infiltrated with AL, thus ^{99m}Tc-PYP scintigraphy is of paramount importance in differentiating AL and ATTR amyloidosis. Assessment is done quantitatively or semi-quantitatively visually. The recommended semi-quantitative visual assessment is graded from 0 to III. While there is no involvement in Grade 0, the involvement in Grade III is more intense than bone involvement. Grade II and III involvement is interpreted as ATTR. In order to make the final noninvasive diagnosis, apart from myocardial involvement, the existence of plasma cell dyscrasia should also be excluded. This is important because a part of Amyloid Light-chain Cardiac Amyloidosis (AL-CA) may present with grade II or higher involvement in bone scintigraphy.[9] Additionally, to distinguish between senile and hereditary ATTR, genetic testing is necessary. If a monoclonal protein is present by immunofixation and/or an abnormal serum free light chain (sFLC) ratio is found, the noninvasive diagnostic pathway is no longer viable, and a biopsy of the involved organ is preferred.[10]

Before the utilization of scintigraphy, cardiac amyloidosis was diagnosed only by histologic confirmation of amyloid deposits through tissue biopsy. It is important to select a biopsy area based on a symptomatic organ rather than the simplicity of the procedure. EMB is not necessary in most patients, as amyloidosis can be diagnosed based on samples collected from alternative tissues such as abdominal fat tissue, rectal mucosa, and minor salivary glands.[11]

In our first case, esophageal biopsy did not have an absolute indication according to recent guideline recommendations. However, due to progressive dysphagia, an endoscopy and esophageal biopsy were performed, which confirmed the already noninvasively diagnosed amyloidosis.

As is already known, clonal diseases such as Monoclonal Gammopathy of Undetermined Significance (MGUS) are common in the elderly population. If pyrophosphate scintigraphy is positive in a patient, TTR and AL amyloidosis can coexist, thus necessitating a tissue biopsy and subtype analysis. In our second case, grade 2 myocardial involvement was detected as a result of bone scintigraphy, and hematologic tests were also positive. The patient, who had proteinuria and renal involvement, underwent a renal biopsy for subtype analysis, and the findings were consistent with AL amyloidosis.

In our third case, the CMRI was consistent with cardiac amyloidosis, and hematologic tests were positive as well. AL-type amyloidosis was predominantly considered as the diagnosis, and a rectal biopsy was performed for diagnosis and subtype analysis. In the diagnostic pathway of AL amyloidosis, biopsy of abdominal fat tissue or affected tissue is recommended due to its higher sensitivity. It would have been more appropriate to follow this pathway instead of the less sensitive rectal biopsy. Upon receiving a negative result from the rectal biopsy, a second biopsy site, myocardium, was selected for its high sensitivity. A positive EMB aided in the final diagnosis of amyloidosis following the negative rectal biopsy result.

Two stages can be identified in the diagnosis of cardiac amyloidosis: the suspicion phase and the definitive diagnosis phase. The suspicion phase involves determining features suggestive of amyloidosis found in the clinical, laboratory, and imaging tests of the patients. The definitive diagnosis stage consists of confirming the diagnosis through invasive or noninvasive methods and identifying amyloid subtypes after diagnosis.

As a result, cardiac amyloidosis, a disease with high mortality and morbidity, is more successfully and effectively treated when diagnosed early. Non-invasive diagnostic methods are becoming widespread due to advancements in technology. According to current algorithms, tissue typing and biopsy site selection are recommended in patients with suspected cardiac amyloidosis, based on clinical and echocardiographic findings, and cardiac involvement is further assessed with subsequent PYP scintigraphy or CMRI. In cases where non-invasive diagnostic methods are insufficient for diagnosing amyloidosis, cardiac or non-cardiac biopsy emerges as an important tool. However, the potential for false-negative results should also be considered.

List 1. Red Flags in Cardiac Amyloidosis[1,5]

Extracardiac	Cardiac
• Polyneuropathy • Dysautonomia • Color change in the skin • Cutis laxa • Macroglossia • Deafness • Bilateral carpal tunnel syndrome • History of ruptured biceps tendon • Lumbar spinal stenosis • Vitreous deposits • Family history • Renal insufficiency • Proteinuria	• Hypotension or regression of hypertension • Pseudoinfarction pattern on ECG • Low QRS voltage despite left ventricular hypertrophy • AV conduction disease • High NT-proBNP values incompatible with heart failure • Consistently high troponin values • Granular appearance in myocardium in echocardiography • Increased right ventricular and valve thicknesses • Pericardial effusion • 'Apical sparing' with reduced longitudinal strain on strain imaging • Subendocardial LGE in CMRI • Increased native T1 values • Increased extracellular volume • Abnormal gadolinium kinetics

Informed Consent: The families of all patients in this case series provided written consent for the publication of their cases.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.B.B., Ö.Ö.T.; Design – G.B.B., Ö.Ö.T.; Supervision – G.B.B., Ö.Ö.T.; Materials – G.B.B., Ö.Ö.T.; Data Collection and/or Processing – G.B.B., Ö.Ö.T.; Literature Review – E.Ö., F.A.D., B.Ö.; Writing – E.Ö., F.A.D., B.Ö.

Conflict of Interest: No conflict of interest disclosure has been received from the authors.

Funding: The authors declared that this study received no financial support.

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