International Journal of Emergency Medicine

CASE REPORT

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Diagnostic and therapeutic challenges in rapidly progressing cardiac amyloidosis: a literature review based on case report

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Abstract

Introduction Cardiac amyloidosis is a rarely reported and potentially fatal variant of the systemic disease. Its early diagnosis could potentially lead to significantly improved clinical outcomes.

Case presentation A 56-year-old female presented with dyspnea and palpitations. Her physical exam and non-invasive evaluation with cardiac magnetic resonance imaging (CMRI) revealed restrictive cardiomyopathy, and the bone marrow biopsy results showed systemic amyloidosis.

Discussion The diagnosis of cardiac amyloidosis is not always straightforward, and delay can cause the progression of the disease and an increased risk of morbidity and mortality. Electrocardiograms, echocardiograms, cardiac magnetic resonance imaging, and histopathologic evaluation are the main methods for diagnosing cardiac amyloidosis. The treatment consists of controlling heart failure symptoms and disease-modifying interventions, including medical and surgical therapeutic methods.

Clinical learning point (conclusion) Cardiac involvement is the main cause of death in systemic amyloidosis. Early suspicion, diagnosis, and treatment are crucial in improving patients' survival. CMRI can play an essential role in the diagnosis of cardiac Amyloidosis. A graphical abstract is provided for visual summary.

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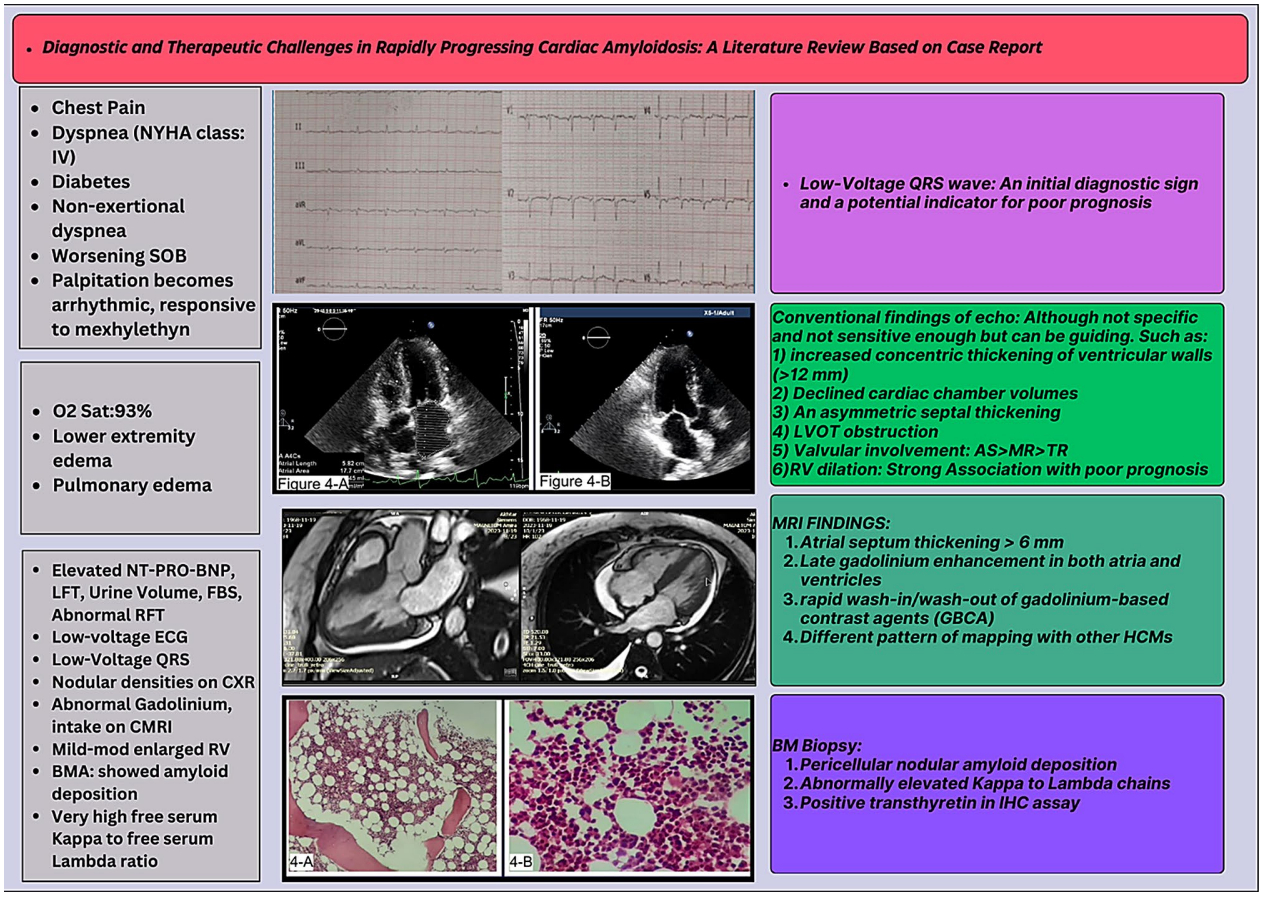
Graphical Abstract



Keywords Cardiovascular imaging, Cardiac magnetic resonance imaging, Amyloidosis, Restrictive cardiomyopathy, Heart failure

Introduction

Amyloidosis is an infiltrative disease involving multiple organ systems. It leads to the deposition of insoluble proteins in the extracellular space and can have several different manifestations [1, 2]. Although there are more than 25 variants of amyloidosis, categorized based on the precursor protein, the cardiac form of the disease is almost always seen in two variants of the amyloid light chain (AL) variant and the less commonly encountered amyloid transthyretin (ATTR) variant [3]. The cardiac variant of amyloidosis is uncommonly reported. It is a restrictive cardiomyopathy caused by abnormal deposition of the misfolded and aggregated proteins in the extracellular myocardium [4]. The AL form is caused by the accumulation of the misfolded immunoglobulin light chains in the context of plasma cell dyscrasia, involving other tissues manifesting as nephrotic syndrome, gastrointestinal diseases, and autonomic nervous system pathologies [5]. However, transthyretin (ATTR) amyloidosis has been caused by the accumulation of a liver-produced protein called transthyretin [6, 7]. This type has been classified into two types: (1) Wild-type ATTR cardiac amyloidosis (ATTRwt), mostly presented as a cardiac-restricted subtype, and (2) hereditary or mutant ATTR cardiac amyloidosis (ATTRm), caused by inherited transthyretin gene mutations. In contrast with the previous one, this form also involves peripheral and autonomic nervous systems, differentiated from each other by the mutation type [3, 8]. Cardiac amyloidosis is rarely reported, affecting 1 in 100,000 individuals [3].

Cardiac involvement is the primary cause of death in systemic amyloidosis, and regardless of the symptoms, it is the main factor reducing the survival of the patient [9, 10]. Timely diagnosis, although not straightforward, is crucial since the delayed diagnosis and progression of the disease may cause an increased risk of morbidity and mortality [11, 12]. The clinical manifestations of cardiac amyloidosis vary largely and range from an incidental

finding during the evaluation of a patient with systemic diseases to manifestation by dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, lower limb swelling, and abdominal distension due to ascites caused by restrictive cardiomyopathy and heart failure. Cardiac symptoms can also be mild and begin with dyspnea on exertion, palpitations, chest pain, presyncope, and syncope caused by the inability of the left ventricle to augment forward stroke volume. as well as reduced diastolic function [1, 13, 14]. On physical examination, patients with cardiac amyloidosis may have periorbital purpura, lower extremity edema, elevated jugular venous pressure (JVP), lung crackles, reduced blood pressure, and ascites [1, 12]. Moreover, systemic findings such as macroglossia, neuropathy, orthostatic hypotension, hepatomegaly, and gastrointestinal bleeding might also be seen [13].

In this study, the history and clinical progression of a 56-year-old female patient diagnosed with cardiac amyloidosis is discussed.

Case presentation

Case history and physical examination

A 56-year-old female with diabetes mellitus (DM) complicated by proteinuria presented with worsening dyspnea (NYHA function class III) beginning two weeks before her initial presentation. Her symptoms were exertional and began to limit her routine daily activities. She had not noticed any specific trigger for the initiation of her symptoms. She was taking Sitagliptin 100 mg/daily.

On her initial physical examination, the patient had stable vital signs (blood pressure: 100/70, pulse rate: 75, and respiratory rate: 18) except for her blood oxygen saturation, which was 93% in ambient air. Her cardiopulmonary examination was notable for decreased breath sounds and a 2+lower extremity pitting edema.

Laboratory and radiological studies

Index laboratory data are summarized in Table 1. The patient was found to have an elevated NT-ProBNP of 2970 (normal range<300). High blood sugar levels, liver enzymes, abnormally elevated kidney function test markers, and increased urine volume and protein secretion levels. An electrocardiogram (ECG) showed low-voltage waves in the limb leads (Fig. 1). Her chest X-ray showed nodular densities, suggesting abnormal deposition (Fig. 2). An echocardiogram showed findings of restricted cardiomyopathy with dilated LA and RA and a mildly reduced LVEF of 45% (Fig. 3; Table 2). A cardiac magnetic resonance (CMR) pattern of gadolinium uptake was indicative of cardiac amyloidosis (Fig. 4). A bone marrow aspiration (BMA) and bone marrow biopsy (BMB) showed amyloid deposition in the bone marrow, suggestive of systemic amyloidosis (Fig. 5). The Kappa and Lambda light chains showed a free serum Kappa to free serum Lambda ratio of 625.92 (Normal range: 0.2–1.65 During her hospitalization, she had an abrupt feeling of palpitation and breathlessness. An ECG demonstrated a polymorphic ventricular tachycardia episode and was treated with Mexiletine. The patient was recommended to undergo a biventricular pacemaker insertion, which she declined.

Two days after her discharge, the patient was taken to another hospital due to loss of consciousness and palpitation and was found to have pulseless VT, for which she received CPR and received post-arrest care.

Outcomes and follow-ups

Despite the patient's critical condition and being a candidate for cardiac catheterization, she did not provide informed consent because she felt the medical procedure was futile. The patient's capacity for decision-making and the suitability of her judgment were evaluated by a psychiatrist, who showed full competency, and she was discharged based on her personal preference. She agreed to initiate the medical treatment with Furosemide 40 mg twice per day to alleviate her symptoms. The patient was visited one and two months later and showed a better clinical condition, less significant subjective dyspnea, blood oxygen saturation of 95, and less severe crackle detected compared to before the initiation of treatment.

Discussion

Although the cardiac variant of systemic amyloidosis has been reported to have a prevalence of as low as 10 in one million people, it is considered the most prevalent type of restrictive cardiomyopathy, followed by cardiac sarcoidosis and cardiac hemochromatosis. Moreover, this disease has been associated with the main cause of mortality in systemic amyloidosis [1]. Therefore, it has high clinical significance, and its diagnosis should be made as soon as possible to control the disease progression and prevent early heart failure and death [12]. Moreover, since this health condition is linked to vague and unspecific symptoms, the diagnosis is rarely made before the acute clinical presentation. These symptoms include exertional dyspnea, fatigue, weakness, exercise intolerance, lower extremity edema, and significant proteinuria in case of kidney involvement. The excreted proteins are mainly composed of albumin and light chains. The diastolic heart failure due to restrictive cardiomyopathy can also be seen in 50% of presented cases [12, 15]. The case presented in this study also demonstrated the mentioned features.

Role of electrocardiogram (ECG) in the diagnosis of cardiac amyloidosis

The diagnosis of cardiac amyloidosis is a multidisciplinary task that should be performed with the

Table 1 Laboratory findings of the patient

Test	Result	Reference Range
RBC (10^6/µl)	4.2	4.2–5.5
Hemoglobin (gr/dL)	11/8	12–16
WBC (per µl)	9700	4.000–11.000
MCV (fL)	88	80–99
Hematocrit (%)	42	37–47
Platelet (per µl)*10^3	169	150–400
Neutrophils (%)	66%	40–75
Lymphocytes (%)	35.1%	20–45
Eosinophils (%)	4.4%	0–6
MCH (pg/cell)	30	27–31
MCHC (g/dL)	32.7	32–36
Troponin I (First sample)	Negative	Negative
lipid profile, coagulation factors, and troponin		
Cholesterol	145	Up to 200
TG (mg/dl)	122	Up to 150
LDL (mg/dl)	90	Up to 130
HDL (mg/dl)	32	> 45 mg/dl
VLDL (mg/dl)	24	2–30 (mg/dl)
T3 (ng/dL)	80	80–190 ng/dL
T4 (µg/dL)	9.0	5.0–12 µg/dL
TSH (mU/L)	1.8	0.4-4.0 mU/L
NT-Pro BNP (pg/mL)	2970	< 300 pg/mL
Parathyroid Hormone (pg/mL)	50	14–65 pg/mL
25 (OH) Vitamine D3 (ng/mL)	26/3	40 to 60 ng/mL
PH	7/40	7.37–7.45
PCO2 (mm Hg)	32	35 to 45 mm Hg
HCO3 (mmol/L)	20	22–32 mmol/L
Sodium (mEq/L)	141	135–145 mEq/L
Potassium (mEq/L)	4/4	3.7–5.2 mEq/L
Viral Marker	Negative	Negative
Fasting Blood Sugar (mg/dl)	318	74–106 mg/dl
LDH (lu/L)	370	235-470lu/L
K^+ (meq/lit)	4.0	3.5-5.3meq/lit
Creatinine (mg/dl)	1/64	0.5-1.00
Urea (mg/dl)	105	13–43
Uric Acid (mg/dL)	8/2	2.7–7.3 mg/dL
Hb A1C %Hb	7	4.8–5.9
PT	13.5 S	11–13 s
PTT	27s	25–38 s
INR	1.19	1-1.5
CK-MB	8	< 25u/l
Troponin I (Second sample in 6 h)	Negative	Negative
ESR (Millimeters per hour)	29	0–20 (Millimeters per hour)
CRP	2+	Negative
AST (U/L)	102	8–33 U/L
ALT (U/L)	189	4–36 U/L
Alkaline Phosphatase (U/L)	252	20–140 U/L
Total Bilirubin (mg/dL)	2/2	0.1–1.2
Direct Bilirubin (mg/dL)	0/6	< 0.3
LDH (U/L)	340 (U/L)	140–280 (U/L)
Urine PH	5	4.5-8
Urine Blood	1+	None
Urine WBC	6–8	0–1

Table 1 (continued)

Test	Result	Reference Range
Urine RBC	8–10	0–1
Urine Culture	Negative	Negative
Anti Double-Stranded DNA	< 100	0-100
ANA	0.1	< 0.2
C3 (mg/dL)	180	88–206 mg/dL
C4 (mg/dL)	30	16–48 mg/dL
CH50 (Hemolytic Units)	100	41–90 Hemolytic Units
Urine Volume 24-hour	4000 ml	800–2000
Urine Creatinine 24-hour	120	52–92 micromoles/L
Urine Protein 24-hour (mg)	3000	< 150 mg

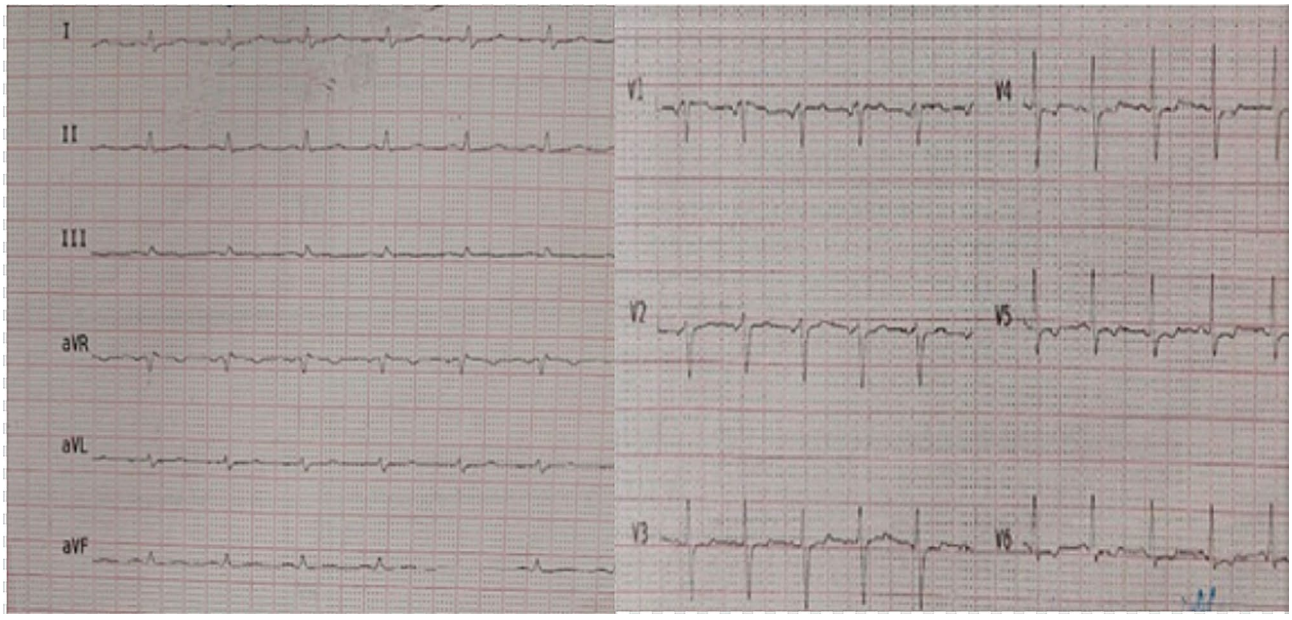


Fig. 1 The electrocardiogram obtained at the patient's presentation Shows low-voltage cardiac waves, which were evident in the limb leads

collaboration of various specialties [1]. Low-voltage criteria on the ECG (QRS voltage amplitude of 1mV in all precordial leads or 0.5mV in all limb leads) is caused by amyloid deposition [16, 17]. Although the definitions for low-voltage QRS might affect the accuracy of CA diagnosis, it has been shown it is a useful marker for the initial work-up of patients who might have CA [18]. Cipriani et al. identified the difference between the prognostic values of low-voltage QRS and different types of CA [19]. They evaluated the pattern of QRS decline in 411 CA patients (AL CA: $n=120$, ATTR CA: $n=291$) and found that the prevalence of low-voltage QRS has been significantly higher in AL CA patients. On the other hand, this electrocardiogram indicator showed a strong association with poor prognosis and noticed that LQRSVs can independently predict a considerable progression of cardiac disease and independently predict the risk of cardiovascular death [19].

Role of echocardiogram in the differentiation of cardiac amyloidosis from other cardiovascular diseases

The deposition of abnormally shaped proteins in the extracellular space of the myocardium can also be presented in non-invasive imaging such as echocardiography and cardiac magnetic resonance imaging [1, 12]. One of the major points that can lead to the diagnosis of CA and its differentiation from other types of HCM is echocardiographic features [20]. There are conventional measures that can guide physicians toward the CA diagnosis. However, these parameters do not have enough accuracy and specificity for the CA diagnosis, particularly in the early CA stages [21, 22]. Although a normal LV diameter does not rule out CA, Echocardiograms commonly show increased concentric thickening of ventricular walls (>12 mm, especially if no other reason has been found or the thickening is disproportionate with the cause) [23, 24], increased echogenicity, septal pseudohypertrophy (can be the only sign seen in the initial

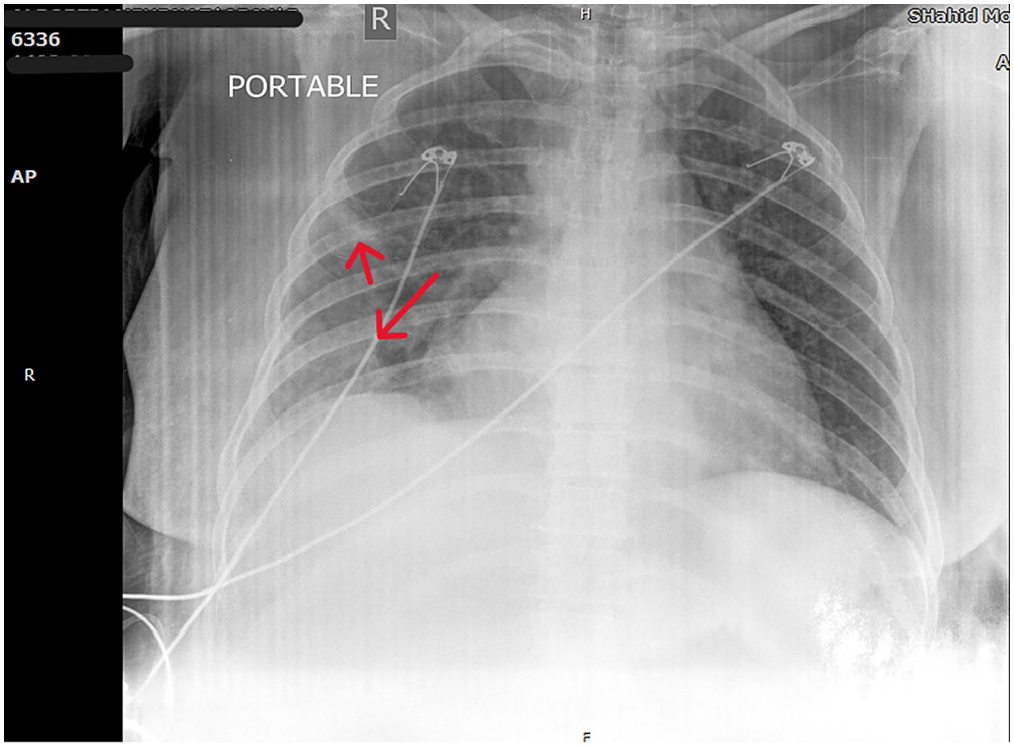


Fig. 2 The patient's chest X-ray showed nodular densities, suggesting amyloid deposition (red arrows)

stages), and declining cardiac chamber volumes [24–26]. An asymmetric septal thickening can also cause LVOT obstruction.

On the other hand, information obtained by modern devices such as Bidimensional speckle-tracking echocardiography (2D-STE), including APS, SAB, and LVEF/GLS, are associated with higher accuracy in diagnosis [22]. Variable cut-offs regarding the diagnosis of CA are calculated based on several echo measures suggested by Boldrini et al. using measures to differentiate IL-CA (Table 3) from TTR-CA (Table 4) [27]. An IWT score has shown high accuracy in diagnosing TTR-CA and AL-CA [21]. Although not completely proven, this measure has been approved by the ESC [23]. Other echocardiographic variables can indicate a higher risk of this diagnosis and become more prominent with the progression of the disease, such as: (1) Typical increased myocardial echogenicity; (2) Increased RV wall thickness, (3) Thickening of the heart valves, (4) Thickening of the interatrial septum, (5) Biatrial dilation, (6) pericardial and pleural effusion. Finally, when the severity gets closer to its climax, an infiltrative restrictive CM becomes evident [28].

Other echocardiogram findings of the CA are extra LV findings such as Interatrial septum and Cardiac valve involvements, which have low specificity but can have practical, beneficial points as well. One of these is increased interatrial wall thickness (>5 mm). These findings are more suggestive of CA if they are accompanied by a myocardial sparkling (hyperreflective texture due to increased myocardial echogenicity) [29]. Moreover, valvular involvement in various valves can be seen in CA, resulting in a significant decline in the patient's capabilities and quality of life. Aortic stenosis (AS), mitral regurgitation (MR), and tricuspid regurgitation (TR) are the most prevalent valvular diseases seen in CA [30]. Considering the mutual pathophysiology, risk factors, and presentation of AS and valvular involvement of CA, the diagnosis is challenging, and those with both conditions simultaneously are more prone to have progressive and severe cardiac diseases [31, 32]. Transcatheter aortic valve replacement (TAVI) can be a useful solution for this patient's condition, which is used based on the patient's condition severity [33].

Different variables are associated with various outcomes. While increased RV size (dilation) is linked to an increased mortality rate and poorer outcomes, gradually elevated LV thickness is associated with an improved prognosis and a higher survival rate [34, 35]. Moreover, increased atrial size has been demonstrated to be a reliable predictor for the progression of heart failure and all-cause mortality [36, 37]. Licordari R. et al., in a study with 37 TTR-mutation-positive patients with and without CA, concluded that RV dimensions were significantly larger in the positive group. Moreover, patients with CA had higher TAPSE, lower CPAP, and lower RV-LS. It has also been shown that there is a correlation between the

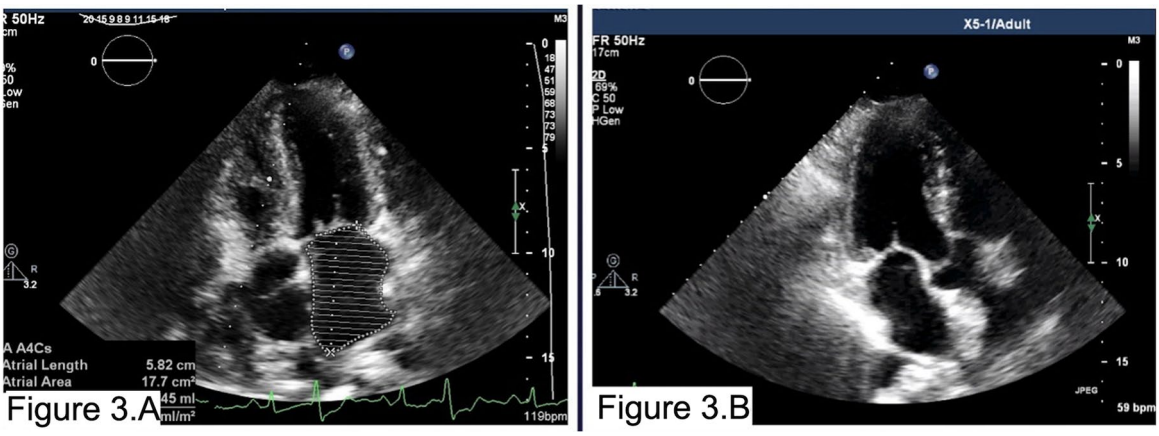


Fig. 3 The echocardiogram findings were suggestive of restrictive cardiomyopathy

Table 2 The patient's echocardiogram showed evidence of restricted cardiomyopathy

Variable	Result
Chambers sizes and ventricular function	Normal size (LVEDD:45 mm), Mild LV systolic dysfunction (LVEF:45%), Severe decreased GLS:-7%, and global hypokinesia, Moderate-Severe LVH, LVSD:16.5 mm and PWP:15mmHg (Fig. 3C)
	Grade III diastolic dysfunction (E/A > 2, E/Ea > 15, and E":3Cm/S), Mild LAE (LAVI:35cc/m^2), Mild RAE (RA area: 18cm^2) (Fig. 3D)
	Mild RVE and Moderate RV systolic dysfunction (TAPSE:12 mm), FAC:20%,
Valves	Trileaflet AV, No AS, No AI, Normal ascending aorta and root, No COA, No MS, Moderate MR, Moderate TR (TVG:31 mmHg, PAP:41mmHg), No TS
IVC size	Top normal of normal size IVC and respiratory collapse < 50%
Pericardial Effusion	Moderate PE (12 mm around RA), Small PE with no compressive sign
Recommendation	According to the findings, RCM should be considered, and CMR is recommended

LVEDD: Left ventricle end-diastolic diameter, LVEF: Left ventricle ejection fraction, GLS: Global longitudinal strain, LVH: Left ventricle hypertrophy, LVSD: Left ventricle systolic diameter, PWP: Pulmonary wedge pressure, E/A: E-wave on A-wave ratio, LAE: Left atrial enlargement, LAVI: Left-atrial volume indexed, RAE: Right atrium enlargement, RVE: Right ventricle enlargement, TAPSE: Tricuspid annular plane systolic excursion, FAC: Fractional area change, AV: Aortic valve, AS: Aortic stenosis, AI: Aortic insufficiency, COA: Coarctation of Aorta, MS: Mitral stenosis, MR: Mitral regurgitation, TVG: Tricuspid valve gradient, PAP: Pulmonary Atrial Pressure, TS: Tricuspid stenosis, IVC: Inferior vena cava, RCM: Restricted cardiomyopathy, CMR: Cardiac magnetic resonance, E/A: E-wave to A-wave ratio, E':Ventricle relaxation index

severity of the RV enlargement and CA progression, and those with larger RVs had more critical clinical conditions related to their CA [38]. In another trial, Mozan C et al. compared 315 patients, including 105 CA patients, and noticed that Free-wall right ventricular longitudinal strain (FWRVLS) has a strong diagnostic and prognostic value in the diagnosis and workup of patients with light chain CA and gets worse with the progression of CA [39].

Role of cardiac magnetic resonance imaging (CMRI) in the diagnosis of cardiac amyloidosis

Cardiac MRI can play a substantial role in the diagnosis of CA and the differentiation of its subtypes. Cardiac MRI can also reveal the extracellular amyloid deposition around the myocytes and valvular thickening. Two specific features are seen in the involvement of the heart in amyloidosis atrial septum thickening>6 mm and the late gadolinium enhancement in both atria and ventricles [40–42]. These features were also seen in our patient's cardiac MRI. Features, such as declined signal intensity on T1 and T2 sequences, have shown an association with clinical outcomes. Moreover, cardiac MRI can be a useful tool for discriminating CA from other hypertrophic myocardium by several different characteristics between these two types of patients, such as the pattern of involvement of various structures mentioned above in CA and other HCMs. Another practically beneficial aspect of using MRI is using their modern techniques, which have become very practical in all fields of medicine [43]. An imaging modality developed for identifying ischemic and non-ischemic cardiac tissue is late-gadolinium (LGE) MRI, which is the established CMR technique for characterizing cardiac tissue [44]. The difference between CA and CMRI is an "early darkening" pattern, a clear darkening of the LV cavity seen in CA. This process is called a rapid wash-in/wash-out of gadolinium-based contrast agents (GBCA) [45]The other type of cardiac MRI modality used for diagnosing CA is Mapping, which is currently used for diagnosing CA. The area under the curve (AUC) for detecting CA is evaluated by Karamitsos et al. and showed a perfect performance in the definite or possible cardiac involvement (0.97) [46]. These features

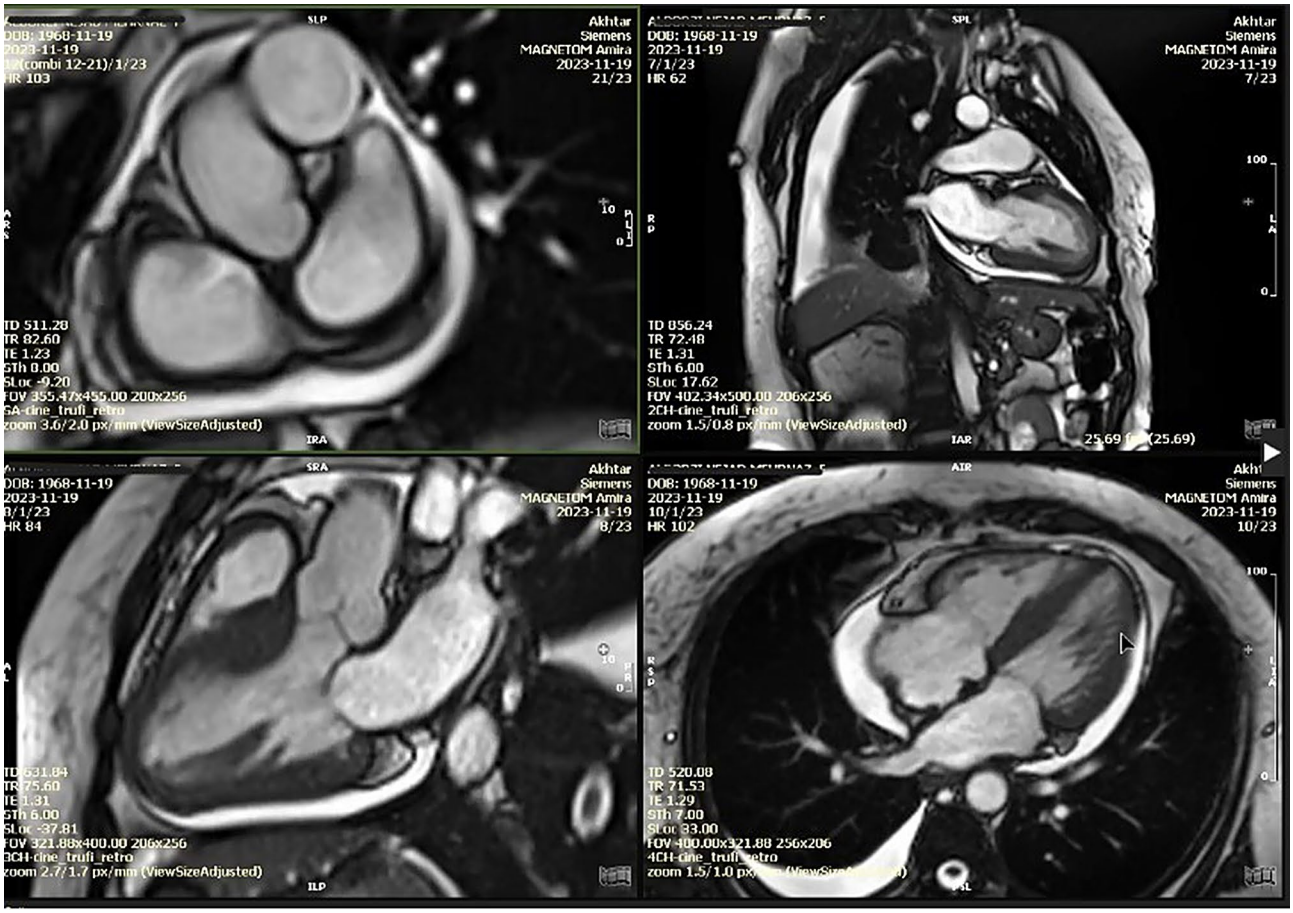


Fig. 4 Cardiac MRI showed evidence of restricted cardiomyopathy suggestive of cardiac amyloidosis. The left and right atrium were high-normal in size (LA area: 19cm^2, LA area index: 11 cm^2/m^2, RA area: 22cm^2, RA area index: 12 cm^2/m^2), and the LAS was hypertrophied. LV hypertrophy (maximal septal thickness 14 mm in the inferoseptal area) and a mild reduced LV systolic function (LV ejection fraction: 46%, and LV end-diastolic volume:100 ml) could be seen. Mild RVH and mild reduced RV systolic dysfunction could also be detected (RV ejection fraction: 43% and RV end-diastolic volume: 100 ml). Moreover, mild mitral regurgitation, mild tricuspid regurgitation, and mild mitral thickness were demonstrated in the valvular evaluation. The main pulmonary artery was mildly dilated (13 mm). Moderate left-sided pleural effusion was obvious, with evidence of mild pericardial effusion (anterior LV side: 6 mm and inferior LV side: 9 mm) without any compressive effect on the LV or RV. In the gadolinium phase, diffuse subendocardial to transmural enhancement is achieved throughout LV and RV and bilateral walls and enhancement of inter-atrial septum and atrioventricular valves

can also evaluate the response to treatment [12]. Nuclear SPECT (single-photon emission computed tomography) has shown the ability to differentiate AL-type amyloidosis from the ATTR variant. While radioisotope uptake is very poor in AL amyloidosis, a strongly positive bone tracer cardiac scintigraphy has been associated with TTR amyloidosis [47].

Naturetic peptides reflect filling pressure, not the Dx of amyloid. One of the main features of the diagnosis is blood markers. Specifically, the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), a biomarker linked to cardiac dysfunction and heart failure, is useful for diagnosing cardiac amyloidosis. This biomarker is elevated regardless of the amyloidosis subtype [48]. The laboratory data evaluated in our patient have also demonstrated elevated NT-pro BNP, suggestive of restrictive cardiomyopathy and diastolic dysfunction. Other guiding biomarkers are cardiac troponin I (cTnI) and cardiac troponin T (cTnT) levels, which are elevated in cardiac tissue injury and inflammation cases. Elevated high-sensitivity cardiac troponin T (hscTnT) is associated with an elevated mortality rate, declined LVEF, and an increased left ventricular wall thickness in AL amyloidosis [49, 50].

The differentiation between AL and ATTR, cardiac amyloidosis types, is done by histologic evaluation. Their different fibril deposition, a pericellular or reticular pattern in AL amyloidosis, and a patchy infiltrate in ATTR can be a hint for distinguishing these two types [51]. For the histopathologic evaluation, the biopsy can be obtained from the abdominal fat pad or salivary glands as a minimally invasive procedure [15]. In the presented case, considering that the diagnosis had been made with less minimally invasive diagnostic methods (CMR and

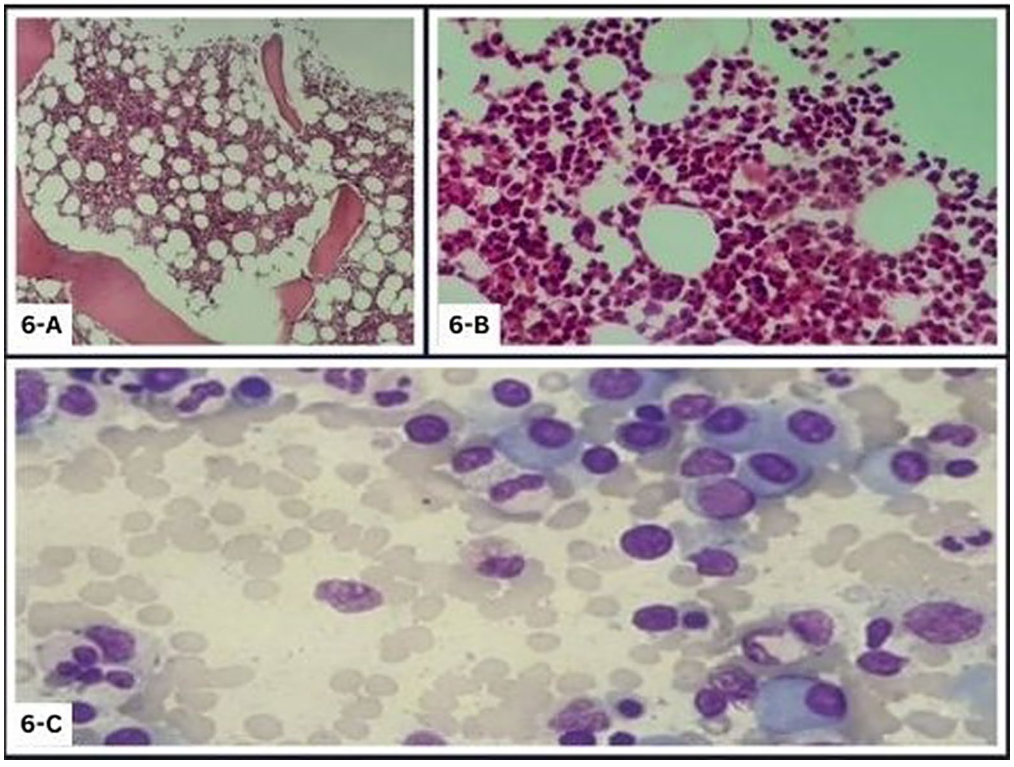


Fig. 5 The bone marrow biopsy of the patient showed amyloid deposition, confirming the provisional diagnosis of systemic and cardiac amyloidosis

Table 3 Variable cut-offs for the calculation of the AL

Index	Cut-off	Point
RWT	> 0.52	2
E/e´	> 10	2
TAPSE	≤ 19 mm	1
GLS	≥ −14%	1

The sum of the above scores has shown to be indicative of AL-CA if > 5

AL: light-chain; IWT: increased wall thickness; CA: cardiac amyloidosis; RWT: relative wall thickness; E/e´: ratio of the early (E) to late (A) ventricular filling velocities; TAPSE: tricuspid annular plane systolic excursion; GLS: global longitudinal strain; SAB: septal apical-to-basal longitudinal strain ratio

Table 4 Variable cut-offs for the calculation of the IWT

Index	Cut-off	Point
RWT	> 0,6	3
E/e´	E/e´ > 11	1
TAPSE	≤ 19 mm	2
GLS	≥ −13%	1
SAB	> 2.9	2

The sum of the above scores has shown to be indicative of TTR-CA if > 8

BMB), burdening these invasive procedures was not clinically indicated and was not performed.

The treatment of cardiac amyloidosis consists of two parts: symptomatic therapy and the treatment of amyloidosis. Fluid and salt restriction coupled with medical therapies are the mainstay of the management of volume overload [12]. This treatment is more sensible in cases of albumin loss due to kidney involvement. In severe cases, repetitive thoracocentesis might be required for the management of pleural effusions [52, 53]In contrast with patients with heart failure without RCM, these patients do not tolerate angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), which can cause hypotension. Therefore, diuretics and aldosterone antagonists are mainly used to manage HF in these patients, along with close monitoring of kidney function, which might be affected simultaneously by drugs and systemic amyloidosis [54, 55].

One of the common complications of this restrictive disease is arrhythmias. It can present as bradyarrhythmia due to the disruption of electrical impulse propagation by the thickened myocardium or as tachyarrhythmia due to the impairment of the conductive system and ventricles caused by the excessive deposition of abnormal proteins [56]. Considering the high risk of digoxin toxicity (binding of medication to deposited fibrils) and intolerability to beta blockers in most cardiac amyloidosis patients, amiodarone is more commonly used. Catheter ablation can be considered in atrial flutter despite its high risk of disease recurrence. A biventricular pacemaker is recommended in cases of atrioventricular block [1]. In the advanced cases, cardiac pacing is indicated. The indications include 1) bradyarrhythmias with a PR interval > 200 ms, QRS duration > 120 ms − History of atrial fibrillation − Long HV intervals in electrophysiologic testing, high degree AV block, and ATTR cardiac amyloidosis. In

tachyarrhythmias, cardiac pacing would be considered if the laboratory evaluation reveals increased NTproBNP, elevated high sensitivity cTnT, decreased glomerular filtration rate (GFR), late gadolinium enhancement, or positive history of syncope [56]. The patient presented in this study had several indications for the implantation of a cardiac pacemaker. However, she refused to undergo the implantation surgery.

On the other hand, the latter part of treatment, which is disease-modifying, is based on normalizing circulating free light chains, which is mostly achieved through stem cell transplant in AL amyloidosis [12, 57]. In contrast, selective proteolytic cleavage is shown to be the main cause of this condition in ATTR subtypes. Two main therapeutic options in these patients are tetramer stabilizers (diflunisal and tafamidis) and TTR silencers (patisiran), which have been shown to be effective in the management of these diseases and also reduce the mortality [12, 58]. A high rate of disease recurrence has been witnessed in orthotropic heart transplants in AL amyloidosis. However, a careful selection of targeted patients, along with intensive chemotherapy for plasma cells after the heart transplant, can result in a desirable clinical outcome [1]. Immunotherapy with medications such as Daratumumab, a CD38 antibody used in combination therapies for multiple myeloma, has been associated with improved conditions in cases of relapsed or refractory diseases [59, 60].

Clinical learning point (conclusion)

Cardiac Amyloidosis is the main cause of death due to systemic amyloidosis despite its rare presentation. The physician's alertness to the symptoms and the association between the systemic and cardiac symptoms could save the patients from early death and improve their survival substantially by initiating medical and surgical treatment. The management of heart failure and arrhythmia is not always straightforward in these patients, and the use of diuretics for the resolution of water retention and amiodarone, along with cardiac pacemakers, are the mainstay of the treatment.

Abbreviations

AI	Aortic Insufficiency
AL	Light Chain
AS	Aortic Stenosis
BMA	Bone Marrow Aspiration
BMB	Bone Marrow Biopsy
CA	Cardiac Amyloidosis
CMR	Cardiac Magnetic Resonance
COA	Coarctation of Aorta
E/A	E-Wave to A-Wave Ratio
E′	Ventricle Relaxation Index
ECG	Electrocardiogram
FAC	Fractional Area Change
FWRVLS	Free-Wall Right Ventricular Longitudinal Strain
GLS	Global Longitudinal Strain
HCM	Hypertrophic Cardiomyopathy
IWT	Increased Wall Thickness
JVP	Jugular Venous Pressure
LAE	Left Atrial Enlargement
LAVI	Left-Atrial Volume Indexed
LV	Left Ventricle
LVEDD	Left Ventricle End-Diastolic Diameter
LVEF	Left Ventricle Ejection Fraction
LVSD	Left Ventricle Systolic Diameter
MR	Mitral Regurgitation
MS	Mitral Stenosis
NYHA	New York Heart Association
PAP	Pulmonary Atrial Pressure
PWP	Pulmonary Wedge Pressure
RAE	Right Atrium Enlargement
RCM	Restricted Cardiomyopathy
RVE	Right Ventricle Enlargement
RVH	Right Ventricle Hypertrophy
RWT	Relative Wall Thickness
SAB	Septal Apical-to-Basal Longitudinal Strain Ratio
TAPSE	Tricuspid Annular Plane Systolic Excursion
TTR-AT	Transthyretin-Amyloidosis
TTRm	Transthyretin-Mutants
TTRwt	Transthyretin-Wild Type
TVG	Tricuspid Valve Gradient
2D-STE	Bidimensional Speckle-Tracking Echocardiography

Acknowledgements
None.

Author contributions
NS, RN, PE, and HS contributed to the Conceptualization, Resource data curation and analysis, project administration, and writing of the initial draft. KH, HT, MT, and RS contributed to the supervision, validation, visualization, investigation, methodology, software, and revision of the final draft of the manuscript. All authors read and approved the final manuscript.

Funding
No funds were received for this study.

Data availability
Data is available on request due to privacy/ethical restrictions.

Declarations

Ethical approval
Not applicable.

Consent to participate
The patient provided written informed consent to participate in this clinical case report, ensuring that all personal information and medical data will be kept confidential and used solely for research purposes.

Consent for publication
The patient provided informed consent for the publication of this report, and the center's ethical policy performed the procedure.

Competing interests
The authors declare no competing interests.

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Received: 23 July 2024 / Accepted: 9 October 2024
Published online: 21 October 2024

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