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Case Report

Long-Term Prognosis of AL Amyloid Cardiomyopathy: A Four-Year Follow-Up from Early Echocardiographic Diagnosis

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Abstract

AL amyloid cardiomyopathy is one of the most concerning differential diagnosis in patients presenting with symptoms of heart failure (dyspnea, leg edema), and preserved or slightly reduced ejection fraction because early recognition and diagnosis of AL cardiac amyloidosis are crucial to stop the disease's progression and prevent irreversible outcomes.

When these patients present solely with heart failure (HF) symptoms but have not yet been diagnosed as having AL amyloidosis (plasma cell disorders: multiple myeloma or light chain deposition disease), they are usually referred to cardiologists. Hence, any delay by the cardiologist in diagnosing AL amyloidosis as a potential cause for this cardiomyopathy can lead to increased mortality and morbidity of these patients since survival is typically around 9 months to 2 years after diagnosis if diagnosis was late; however early diagnosis can improve survival with new targeted therapy for AL amyloidosis.

In this case report we present a 4 and a half years follow-up on a 67 years old man who was diagnosed with AL amyloid cardiomyopathy using transthoracic echocardiography. Early diagnosis of multiple myeloma and AL amyloidosis in this patient was possible due to suspicion of cardiac amyloidosis on echocardiography, including left ventricular hypertrophy with sparkling appearance of the myocardium, dilated atria, elevated filling pressure by pulsed Doppler echocardiography, reduced global longitudinal strain with relative apical sparing, and preserved ejection fraction. As a result, targeted therapy was initiated very early and the patient is still alive and ambulating without assistance 4 years and 6 months after the diagnosis.

Keywords: Heart Failure (HF); Amyloidosis (AL)

Introduction

Amyloidosis is a serious, and progressive infiltrative disease resulting from the accumulation of insoluble clusters of misfolded proteins in tissues, when it occurs at the cardiac level it leads to cardiac amyloidosis, which is often missed as a cause of heart failure [1]; cardiac amyloidosis is a rare and life-threatening condition that has a poor prognosis with severe morbidity and mortality, it is categorized into three main types: light chain amyloidosis (AL), the familial or transthyretin amyloidosis (ATTR) and secondary amyloidosis (AA) with an annual incidence of 1 per 100 000 for AL amyloidosis; cardiac amyloidosis is the most common type of restrictive cardiomyopathy followed by cardiac sarcoidosis and hemochromatosis [2-4].

AL amyloid cardiomyopathy (CMP) often results in a depressed diastolic function in the absence of a left ventricle (LV) dilation or dysfunction, which is known as heart failure with preserved ejection fraction (HFpEF); AL amyloid CMP is considered a HFpEF mimic by the American College of Cardiology Solution Set Oversight Committee [5].

Cardiac amyloidosis is a challenging diagnosis that does not have a single pathognomonic test. Low-voltage ECG combined with echocardiographic features of restrictive cardiomyopathy such as left ventricular hypertrophy in the absence of hypertension, reduced global longitudinal strain with relative apical sparing, high systolic pulmonary artery pressure, pericardial effusion, thickened

leaking valves, preserved or mildly reduced ejection fraction and restrictive Doppler filling pattern of the mitral inflow and tissue Doppler could be strongly suggestive of cardiac amyloidosis; moreover, bone scintigraphy and cardiac magnetic resonance are two other imaging studies used as noninvasive diagnostic modalities for cardiac amyloidosis [2-4].

Besides these noninvasive imaging tests proteinuria, elevated liver enzymes, elevated troponin, and brain natriuretic peptide (BNP) or NT pro-BNP may also be present; in addition monoclonal protein testing such as serum and urine protein electrophoresis and immune-fixation, serum kappa/lambda free light chain, are always positive. Finally diagnosis is made by bone marrow or other special tissue biopsy (endo-myocardial biopsy or biopsy of other involved tissues) with Congo red staining and AL amyloid typing using immunofluorescence [1-3].

The treatment of Cardiac amyloidosis is twofold: the treatment of cardiovascular complications such as heart failure and orthostatic hypotension and the treatment of the underlying condition (AL amyloidosis treatment); diuretics and mineralocorticoid antagonists remain the cornerstone of treatment of heart failure while vasoconstrictors such as midodrine are used to maintain blood pressure and enhance diuresis properly; the treatment of AL amyloidosis itself by chemotherapy agents such as melphalan and cyclophosphamide, and targeted therapy like bortezomib among others [2-4].

Although AL amyloid cardiomyopathy has a poor prognosis with short survival ranging between 6 months and 2 years if not diagnosed early, recent progress in diagnosis and treatment has highlighted the importance of early diagnosis and changes in the management of this disease on morbidity and mortality [6,7]. This case report emphasizes the role of echocardiography in the early non-invasive diagnosis of AL amyloid cardiomyopathy leading to early treatment and better survival [6,7]. This makes cardiac amyloidosis a disease that should be highly suspected when evaluating patient with HFpEF or HFmrEF [5].

Case Report

This is a case of a 67-year-old man, a heavy smoker, who was diagnosed with AL cardiomyopathy by echocardiography 4 and a half years ago. His main presenting symptom was dyspnea which was initially attributed to chronic bronchitis. However, further evaluation by routine transthoracic echocardiography revealed moderate left ventricular hypertrophy, mildly reduced ejection fraction at 43%, elevated filling pressure by pulsed Doppler interpretation of the mitral inflow (E/A>2.03), and low global longitudinal strain (GLS) with typical apical sparing (GLS=-10.3%), these findings prompted the diagnosis of cardiac amyloidosis.

Following the echocardiography, additional tests were ordered, including serum protein electrophoresis, immunofixation, light chain assay, and 24-hour protein electrophoresis plus immunofixation. At that time his metabolic workup was normal with cell blood count with differential (CBCD) showing a white blood cell count (WBC) of 8270 cells/uL, hemoglobin of 11.9 g/dl, and a platelet count of 250 000 cells/uL (Table 1), albumin 32 mg/dl, globulin 27 mg/dl, calcium of 10 mg/dl, creatinine of 0.67 mg/dl (Table 2), electrolytes, liver enzymes and thyroid-stimulating hormone (TSH) were all within normal range. Urine analysis was also conducted and it was negative for proteinuria.

2019	WBC	Hemoglobin	Platelets
Results	8270 g/dl	11.9 g/dl	250,000 cells/uL

Table 1

2019	Creatinine	Calcium	Total serum protein	Albumin	Globulin
Results	0.69 mg/dl	10 mg/dl	59 mg/dl	32 mg/dl	27 mg/dl

Table 2

His imaging did not show any bone lytic lesions, and the patient's heart failure symptoms improved with diuretic therapy using Furosemide 40 mg PO daily and Spironolactone 25 mg PO daily. Serum protein electrophoresis (SPE) showed the presence of a monoclonal peak of 1.8g/L in the gamma region while urine protein electrophoresis was normal.

The results of the serum immunofixation revealed the presence of a monoclonal band of IgG Lambda type in the Gamma region with an abnormal light chain ratio while urine immunofixation was negative for Bence Jones protein.

Confirmation of multiple myeloma (MM) and AL amyloidosis was obtained through bone marrow aspirate and biopsy using Congo red and AL amyloid typing using immunofluorescence (diagnosis made on 22 Oct. 2019). The patient was then started on targeted therapy with Valcade (Bortezomide) at a dose of 1.3mg/m^2/week intravenously along with dexamethasone 40mg daily for 4 days, and Revlimid (Lenalidomide) 25 mg daily from day 1 to 21 on a 28 days regimen was added 18 months later.

His condition remained stable on chemotherapy for around 2 years, until early 2022 during the economic crisis in Lebanon prevented him from receiving treatment due to unavailability and high cost (except for Dexamethasone which he received every week orally). During these 6 months without chemotherapy, his condition rapidly worsened, with increasing heart failure symptoms such as dyspnea due to bilateral pleural effusion, massive ascites, and leg edema. He also experienced severe peripheral neuropathy and autonomic neuropathy, resulting in orthostatic hypotension. These symptoms were treated with high-dose furosemide 250 mg daily orally and Midodrine 5 mg orally 3 times daily. Unfortunately, his creatinine clearance declined, his liver enzymes increased and he developed ascites requiring percutaneous drainage every month. However, he was able to restart chemotherapy as soon as it became available through the Ministry of Health in Lebanon (July 2020). This targeted therapy (Bortezomibe, Lenalidomide) helped to stabilize his clinical heart failure.

2024	WBC	Hemoglobin	Platelets	Creatinine
Results	6590 cell/uL	11.9 g/dl	199 000 cell/uL	0.89 mg/dl

Table 3

His most recent workup in 2024 included various tests that showed normal CBCD (WBC of 6590 cell/uL, Hemoglobin of 11.9g/dL and platelet count of 199 000 cell/uL), Creatinine of 0.89 mg/dl (Table 3), and all other laboratory tests such as electrolytes, liver enzymes, CRP, calcium phosphorus, magnesium, Albumin/Globulin were within normal range.

Protein electrophoresis revealed a decrease in beta1, beta2, and monoclonal peak in the gamma region while urine protein electrophoresis was normal. Serum immunofixation showed restricted gamma IgG heterogeneity and negative urine immune-fixation. His last echocardiogram done 4 years and 6 months after the diagnosis shows.

LVEF stabilized at 44% (Figure 1 and Figure 2).

GLS=-11.1% with apical sparing (Figure 3 and Figure 4).

Left ventricular filling with E/A=1.6 (Figure 5 and Figure 6).

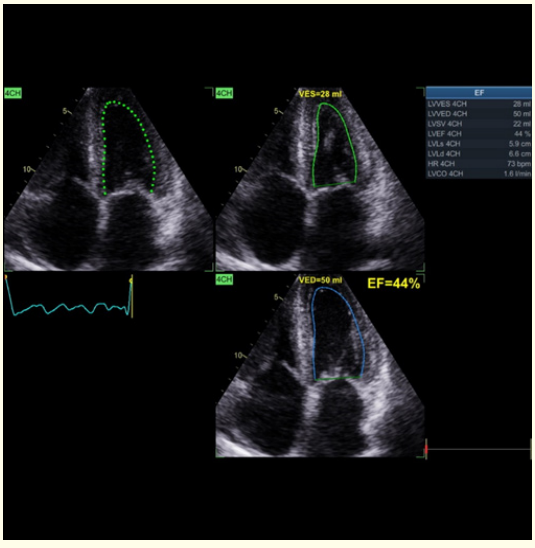

Figure 1

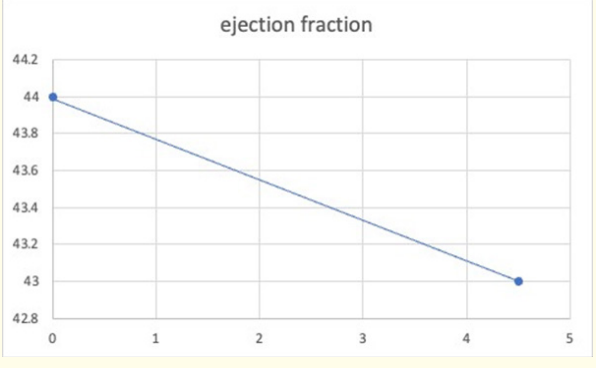

Figure 2

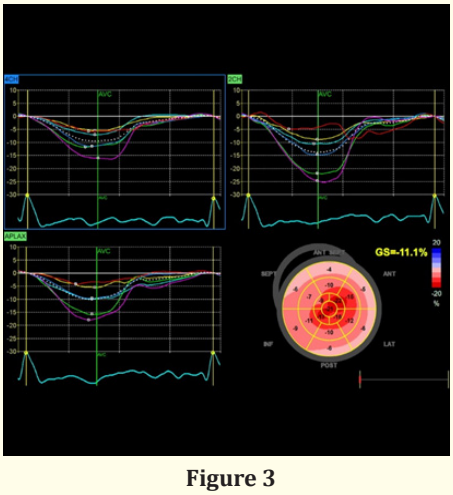

Figure 3

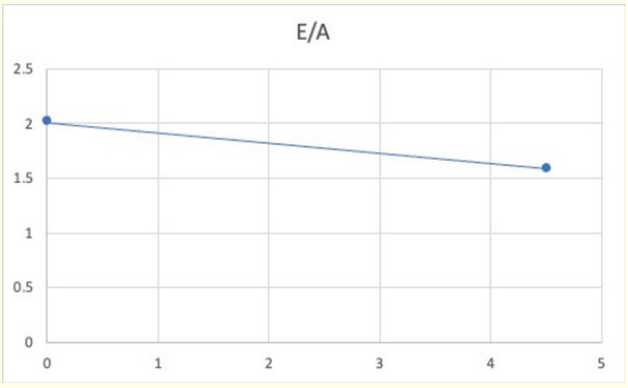

Figure 4

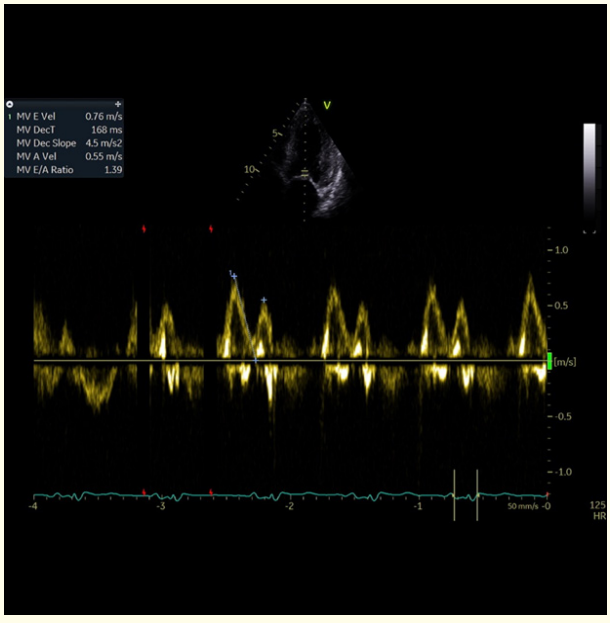

Figure 5

Figure 6

Patient is still ambulating without assistance and with class II NYHA during the writing of this paper.

Discussion

AL Amyloid cardiomyopathy is a very aggressive disease that should be diagnosed early and then managed aggressively to improve clinical outcome [1-3]. Because of HF symptoms these patients usually present to cardiologist, so it is very important that during the examination of these patients, cardiologists should look for signs and symptoms of AL amyloidosis such as signs and symptoms of anemia, bone pain du to lytic bone lesions, neuropathy like carpal tunnel syndrome or spinal stenosis, macroglossia, and sicca if present; it is well known that AL amyloid CMP is associated with neuropathy and that pathology specimen of carpal tunnel ligament and spinal stenosis removed tissue, in these patients, have AL amyloid staining when examined with Congo red and immuno-typing for AL amyloidosis [2-4]. When these patient presents with only symptoms of heart failure, without other disease stigmata like anemia, bone pain du to lytic bone lesions, neuropathy, proteinuria and or renal failure, the probability to make an early diagnosis of AL amyloidosis as a cause of this CMP will be diminished, this is why cardiologist should keep a high degree of suspicion of AL amyloid CMP when performing echocardiographic examination, cardiologist should be aware of the echocardiographic signs of amyloidosis: dilated atria, moderate to severe myocardial hypertrophy and a small left ventricular cavity with sparkling myocardial appearance, thickened valves with mild to moderate leak, a preserved or mildly reduced EF and a mild pericardial effusion; The Doppler signs of elevated LV filling pressure or elevated left atrial pressure like E/A > 2, E/E'> 14, tricuspid regurgitation velocity>2.8m/sec and an LA volume>34ml/m^2. The myocardial longitudinal strain is a powerful tool that helps diagnosing the AL amyloid CMP: with reduced strain, relative apical sparing and an EF/GLS>4.1. The presence of these signs on echocardiography should prompt the diagnosis of AL amyloid CMP [1-3].

Cardiac MR is also a powerful tool for the diagnosis of amyloid CMP but can not differentiate between AL and transthyretin cardiac amyloid; also in the presence of kidney disease gadolinium cannot be administered. Although Technetium Pyrophosphate bone scintigraphy can help in the diagnosis of cardiac amyloidosis it cannot differentiate AL amyloid from transthyretin amyloid CMP but in transthyretin amyloid CMP the myocardial technetium pyrophosphate uptake is much stronger than in AL amyloidosis. Brain natriuretic peptide (BNP), NT pro BNP and cardiac troponin are elevated in AL amyloid CMP [3,4].

It is the serum protein electrophoresis and immune-fixation with light chain assay that will orient to the diagnosis of AL amyloidosis. The diagnosis has to be confirmed with biopsy and immunotyping of bone marrow or other tissues (Congo red staining and AL amyloid typing using immune-fluorescence) [3]. The treatment of AL amyloid CMP consist of treatment of the CMP (Cardiac and vascular complications) and the treatment of AL amyloidosis itself. Treatment of CMP and vascular complications: cardiovascular medications used in heart failure may cause significant hypotension, bradycardia, or worsening of heart failure (HF) in patients with AL cardiac amyloidosis; this is due to binding of drugs to amyloid fibers, unmasking the autonomic neuropathy, leading to poor hemodynamic of HF in these patients; medications like Beta blockers, angiotensin enzymes inhibitors (**ACE inhibitors)**, angiotensin receptor blockers (**ARBs)** and angiotensin receptors blockers plus neprylisin inhibitor(ARNI) are contraindicated [3,4] in patients with AL CMP and poor hemodynamic reserve (orthostatic hypotension); in patients with good hemodynamic reserve and no bradycardia, these medications can be used with caution [3,4]; digoxin should be used with caution, amyloid fibrils bind to digoxin increasing its toxicity regardless of the serum level [9]; inotropic support is helpful in these patients [3,4]; implantable cardioverter-defibrillator (ICD) for secondary and primary prevention can be done in AL CMP [11]; patients with AL cardiac amyloidosis may benefit from placement of a left ventricular assist device (LVAD) but have worse prognosis compared with other patients [10]. Cardiac transplantation can be done in patients with AL CMP [12]; with contemporary management, the median survival for AL cardiac amyloidosis with cardiac involvement is approximately 5.5 years after diagnosis provided that the diagnosis is early [7].

Treatment of AL amyloidosis itself: the targeted therapy for AL amyloidosis has improved and led when started early and promptly to a better survival and quality of life [7]; autologous hematopoietic cell transplantation (HCT) is indicated in AL amyloidosis if : the physiologic age ≤70 years, troponin T <0.06 ng/mL (or hs-Troponin T <75 ng/mL), systolic blood pressure ≥90 mmHg, creatinine clearance ≥30 mL/min (unless on chronic stable dialysis), eastern Cooperative Oncology Group (ECOG) performance status ≤2, New York Heart Association (NYHA) functional status class I or II, no more than two organs significantly involved (liver, heart, kidney, or autonomic nerve), no large pleural effusions, no dependency on oxygen therapy [13]. Bortezomib-based therapy (eg, daratumumab plus CyBorD, cyclophosphamide, bortezomib, dexamethasone) can also be used in all patients with deferral of HCT [14]. Bortezomib, melphalan, and dexamethasone can also be used for AL amyloidosis [15]. Thalidomide plus low dose dexamethasone with or without cyclophosphamide can be used in patients with AL amyloidosis [16]. Revlimide also can be used for AL amyloidosis [17].

It is really impressive to see that despite the patient not being able to receive targeted therapy for 6 months due to the economic crisis in Lebanon in 2022, he improved after he restarted the targeted therapy. This can be attributed to the early diagnosis and targeted therapy he received, as well as his positive response to initial therapy (both hematological and cardiac) and remaining relapse-free for over up to 2 years initially. Early diagnosis the timing of therapy, initial response, and duration of "no relapse period" are crucial predictors of survival in multiple myeloma and AL amyloidosis. Effective therapy can suppress the number of clonal plasma cells, reduce the M para-protein, and further decrease cardiac amyloid deposits.

Conclusion

AL amyloid cardiomyopathy has a poor prognosis, with survival usually ranging between 6 months and 2 years if not diagnosed early. This case report emphasizes the vital role of echocardiography in the early diagnosis of AL amyloidosis cardiomyopathy, leading to prompt treatment and improved survival rates. By utilizing echocardiography, cardiologists can identify specific echocardiographic criteria that allow early intervention and targeted therapy, likely prolong and improve the quality of lives of patients. Thus when performing echocardiography, cardiologists should maintain a high level of suspicion for AL amyloid cardiomyopathy. If there is any suspicion of AL amyloid cardiomyopathy by echocardiography it is recommended to request protein electrophoresis and immunofixation in serum and urine with light chain assay. Cardiologists should also be on the lookout for other symptoms such as neuropathy (Carpal tunnel, spinal stenosis) and macroglossia which were not initially present in our patient. Additionally, for the other major treatable cause of cardiac amyloidosis, transthyretin cardiomyopathy, a pyrophosphate Technetium bone scan can be conducted after the results of AL amyloidosis workup.

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