Case Report

Multiple Myeloma Presenting as Cardiac Amyloidosis With Biventricular Failure: A Case Report

Ajinkya Rahatgaonkar[1]; Prativa Sethi[1], MD; Prasan Kumar Panda[1*], MD; Shalini Singh[1], MD

ABSTRACT

Cardiomyopathies related to amyloidosis are recognized as a type of infiltrative disorder; however, the degree of infiltration does not align with the severity of hemodynamic impairment. We present a case involving an elderly woman without any known comorbidities or substance use history who presented with congestive heart failure at our hospital. She had been treated with long-term diuretic therapy for heart failure by various physicians. A strong suspicion of primary cardiomyopathy was maintained given the absence of prior comorbidity after a comprehensive medical history review and examination. Two-dimensional echocardiography, protein electrophoresis, and bone marrow examination collectively revealed cardiac amyloidosis secondary to plasma cell dyscrasia. Standard heart failure treatment was initiated alongside chemotherapy; nonetheless, the patient experienced sudden cardiac death at home during follow-up. This case underscores the importance of early diagnosis and treatment of heart failure for patients with cardiac amyloidosis, and it also brings attention to the fact that cardiac amyloidosis can be the first sign of multiple myeloma. ***(Iranian Heart Journal 2024; 25(3): 72-79)***

KEYWORDS: Amyloidosis, Cardiomyopathy, Heart failure, Plasma cell dyscrasia

[1] Department of Medicine and [2] Department of Pathology, All India Institute of Medical Sciences (AIIMS), Rishikesh, India.

*** Corresponding Author:** Prasan Kumar Panda, MD; Department of Medicine and 2Department of Pathology, All India Institute of Medical Sciences (AIIMS), Rishikesh, India.
Email: motherprasanna@rediffmail.com **Tel:** +919868999488

Received: January 20, 2024 **Accepted:** March 29, 2024

Cardiac amyloidosis is a rare and potentially fatal condition marked by the abnormal deposition of amyloid proteins in cardiac tissue. Amyloidosis is a category of disorders unified by the formation of amyloid fibrils, wherein normally soluble proteins misfold and aggregate into insoluble fibrils. These fibrils progressively accumulate in various organs, including the heart, impairing normal function and potentially causing severe complications. Several amyloid proteins can result in cardiac amyloidosis, with the most prevalent forms being immunoglobulin light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis. AL amyloidosis is associated with plasma cell dyscrasia, often occurring in the context of multiple myeloma, whereas ATTR amyloidosis may be hereditary (hATTR) or acquired (wild-type or senile ATTR) due to mutations in the transthyretin gene or the natural aging process, respectively. The clinical presentation of patients with AL amyloidosis exhibits significant variability depending on the affected organs, encompassing

conditions such as nephrotic syndrome, restrictive cardiomyopathy (RCMP), peripheral neuropathy, hepatomegaly, macroglossia, and purpura with skin manifestations. In AL amyloidosis, the most frequently affected organs include the kidney (70%), heart (60%), hepatomegaly with or without splenomegaly (70%), peripheral nervous system (20%), and autonomic nervous system (15%), followed by the gastrointestinal system. Cardiac involvement often results in diastolic dysfunction, and as the disease progresses, systolic dysfunction emerges, accompanied by symptoms of congestive heart failure.[1] Patients commonly present with palpitations, syncope due to arrhythmia or heart block, and angina or infarction.

We present a case involving a postmenopausal female who exhibited signs and symptoms of heart failure, and subsequent evaluation revealed a diagnosis of multiple myeloma with cardiac amyloidosis.

CASE REPORT

A postmenopausal woman in her 60s, without any prior known comorbidities or history of substance use or abuse, presented with complaints of insidious onset, gradually progressive dyspnea for the past 8 months. Initially, dyspnea was only present during exertion but progressed to dyspnea during day-to-day activities over 6 months, accompanied by paroxysmal nocturnal dyspnea. For the past 2 months, she experienced dyspnea at rest, along with orthopnea. There was no seasonal variation in dyspnea, wheezing, cough, expectoration, fever, chest pain, palpitation, or syncope. The patient had been hospitalized 3 times in the previous 6 months for worsening dyspnea at rest and was treated with oxygen support and diuretics, resulting in temporary symptom improvement. Nonetheless, the patient was noncompliant with medications. Additionally, she reported insidious onset, gradually progressive, painless symmetrical abdominal distension, and painless progressive bilateral pitting pedal edema for the past 3 months, associated with decreased urine output for the previous 6 days. There was no reported history of tuberculosis, fever, jaundice, altered mental status, melena or hematemesis, dysuria, frothy urine, hematuria, oral ulcers, Raynaud's phenomenon, or joint pain. Additionally, no history suggestive of coronary artery disease was present. The patient had no family history of similar conditions, premature cardiovascular death, or sudden cardiac arrest, and there was no reported exposure to smoke.

Upon presentation, the patient was in cardiogenic shock, exhibiting a pulse rate of 120 beats per minute, blood pressure of 84/60 mm Hg in the supine position, and a respiratory rate of 30 breaths per minute. Raised jugular venous pressure, distended neck veins, and bilateral pitting pedal edema were observed. Upon respiratory examination, her trachea was observed to be centrally located. Auscultation revealed bilateral crepitations in the infrascapular, interscapular, and axillary areas, accompanied by decreased air entry in the bilateral infrascapular regions and a dull percussion note, suggestive of bilateral pleural effusion with pulmonary edema. The initial diagnosis was congestive heart failure, and treatment was promptly initiated for acute decompensated heart failure. Routine and advanced investigations uncovered thrombocytopenia, mild transaminitis, pre-renal acute kidney injury, and hypergammaglobulinemia (Table 1). The patient tested positive for anti-HCV antibodies, with a very high HCV RNA copy level. Chest X-ray imaging revealed cardiomegaly and bilateral pleural effusion (Fig. 1 A). ECG demonstrated a low-voltage QRS complex (Fig. 1 B). Elevated BNP

levels (>800) indicated heart failure. High-resolution computed tomography of the thorax suggested cardiogenic pulmonary edema, areas of mosaic attenuation, and scattered lung cysts (Fig. 1 C & D). Abdominal ultrasound revealed a prominent, non-collapsing inferior vena cava and hepatic veins, along with moderate ascites. Diagnostic ascitic tap demonstrated high serum-ascites albumin gradient and high protein ascites, indicating a cardiac etiology for the ascites. Pleural effusion analysis confirmed a transudative nature. Two-dimensional echocardiography demonstrated RCMP with sparkling septum, grade 3 left ventricular (LV) diastolic dysfunction, and global hypokinesia with a left ventricular ejection fraction (LVEF) of 15% (Fig. 2 A & B). In the absence of a family history suggestive of RCMP, an evaluation for non-familial causes was conducted. The patient was nondiabetic, with a hemoglobin A1c (HbA1c) level of 5.9%. Hemochromatosis was excluded as a potential cause due to a normal ferritin level of 200 mg/dL. Serum protein electrophoresis revealed a monoclonal gammopathy (M spike) in the gamma globulin region (Fig. 2 C & D), with an elevated lambda free light chain level of 3645.13 mg/L (reference range: 5.71–26.30). Beta-2 microglobulin levels were also elevated at 11915 ng/mL (reference range: 609–2366). Suspecting plasma cell dyscrasia, a bone marrow aspiration biopsy was performed, revealing 30% plasma cells scattered interstitially with focal aggregates that stained positive for CD138 (Fig. 2 E & F). The 24-hour urine protein level was within the normal range. ATTR amyloidosis was excluded as a potential cause due to normal findings on a nuclear scan. An abdominal fat pad biopsy did not demonstrate amyloid deposits.

During her hospital stay, the patient experienced a sudden deviation of the angle of her mouth to the right side, accompanied by the loss of the left nasolabial fold and forehead wrinkles, indicating lower motor neuron-type facial nerve palsy. An urgent neurological consultation was requested, and a magnetic resonance imaging (MRI) stroke protocol was performed, yielding normal results. Bilateral compound muscle action potential latency and amplitude were found to be comparable in the facial nerve study. Upon ENT evaluation, no signs suggestive of herpes infection were observed. Facial nerve palsy in this patient was attributed to AL amyloid deposits. A cardiac MRI was planned; however, it could not be performed due to the patient's persistent orthopnea despite optimal diuresis. The cardiac MRI was rescheduled for a follow-up visit.

Table 1: Investigations During the Hospital Stay

Investigation	Normal Range and Units	Day 1	Day 5	Day 10	Day 11	Day 12	Day 16	Day 18
Hemoglobin	13-17 g/dl	12.3	12.2		11.6			
Total leucocyte count	4-11 x 10^3/uL	7.54	7.99		6.77			
Neutrophil	40-70%		62.3/28/8.2		58/27/12			
Lymphocyte	20-40%	211	200K		198k			
Monocyte	2-8%	1.26	0.64		1.09		1.10	
Eosinophil	1-6%	0.36	-		-		-	
Basophil	<2%	34	34		34		40	
Platelet	150-400x10^3/uL	62	72		-		67	
Serum glutamic oxaloacetic transaminase	0-50 U/L	111	89		90		121	
Serum glutamate pyruvate transaminase	0-50 U/L	95	78		80		98	
Total protein	6.0-8.0 mg/dL	7.8	7.2		7.2		7.5	

Albumin	3.5-4.2 mg/dL	3.5	3.4		3.1		3.2	
Globulin	2.0-3.0 mg/dL	4.3	3.8		4.1		4.3	
Urea	17-43 mg/dL	82	60	69	69	81	152	112
Creatinine	0.72- 1.18 mg/dL	1	0.77	0.91	1.02	1.40	1.98	1.09
Sodium	136-146 mmo/L	139	132	137	141	130	128	125
Potassium	3.5- 5.1 mmo/L	3.9	3.4	3.4	3.1	3.54	4.8	4.7
Chloride	101- 109 mmol/L	96	103	93	83	90	86	81
Calcium	8.6- 10.6 mg/dL	8.9	9.7	9.4	9.3	8.9	9.2	9.1
Uric Acid	3.2- 7.2 mg/dL	9.7	9.6	9.6	9.9	10.7	9.8	6.4
Phosphorus	2.5- 4.5 mg/dL	4.1	3.5	3.3	3.7	4.1	3.9	1.3
Serum Protein Electrophoresis	Hypoalbuminemia was present. Monoclonal gammopathy (M spike) was seen in the gamma globulin region. • Immunoglobulin IgA: 170.18 mg/dL (40-350) • Immunoglobulin IgG: 3413.00 mg/dL (650-1600) • Kappa, free light chain: 132.77 mg/L (3.30-19.40) • lambda, free light chain: 3645.13 mg/L (5.71-26.30) • FLC ratio: 0.036 • Beta-2 microglobulin: 11915 ng/mL (609-2366)							
Bone Marrow Biopsy	Marrow spaces exhibited normocellularity for age with an overall cellularity of 50% and mild erythroid prominence, characterized by normoblastic maturation. Numerous plasma cells, which stained positive for CD138, were observed scattered interstitially, as well as in focal aggregates. Plasma cells comprised 30% of the marrow nucleated cells.							
Abdominal Fat Pad Biopsy	Fibrofatty tissue with blood vessels was observed, and no amyloid deposits were identified.							

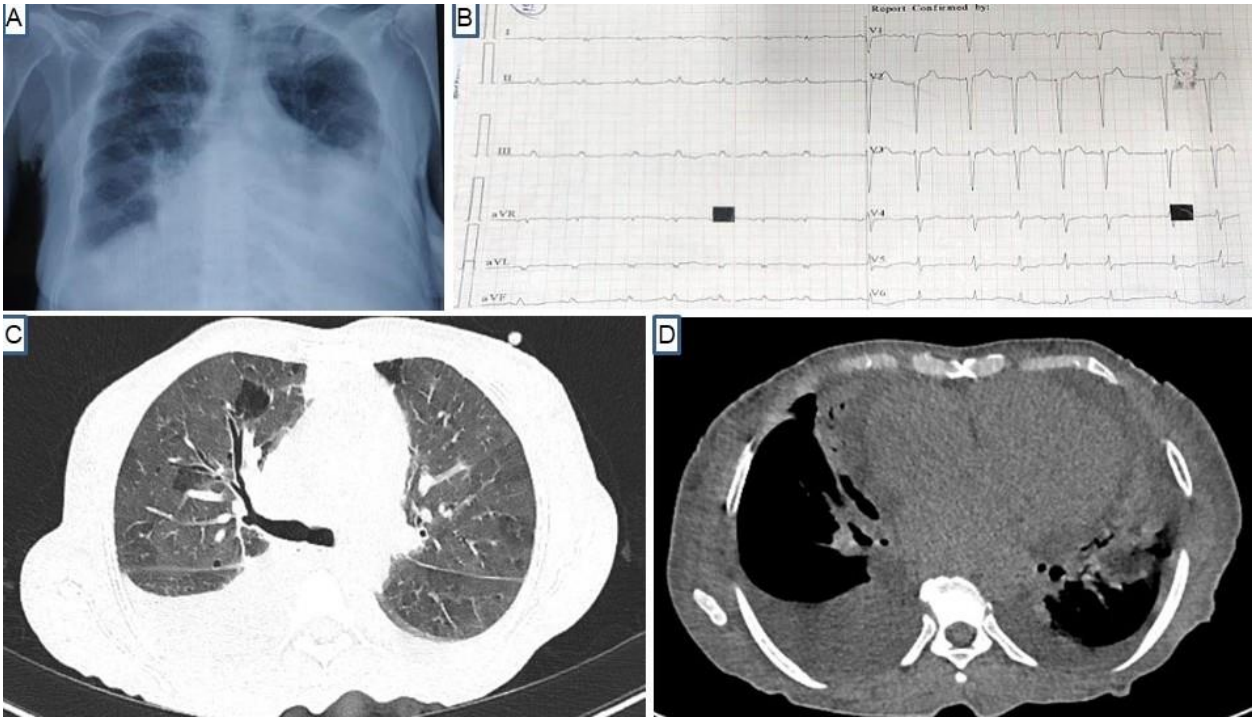

Figure 1: Chest imaging including ECG are presented herein. (A) Chest X-ray (PA view) shows cardiomegaly, bilateral pleural effusion (left more prominent than right), and cephalization of blood flow. (B) Twelve-lead ECG demonstrates right axis deviation, low voltage QRS complex in all limb leads, poor progression of QRS, and T-wave inversion in chest leads V5-V6. (C) The high-resolution computed tomography chest (sagittal view; lung parenchymal window) illustrates areas of bilateral mosaic attenuation and ground-glass attenuation, suggestive of cardiogenic pulmonary edema with scattered lung cysts. (D) The high-resolution computed tomography chest (sagittal view; mediastinal window) depicts cardiomegaly with bilateral pleural effusion.

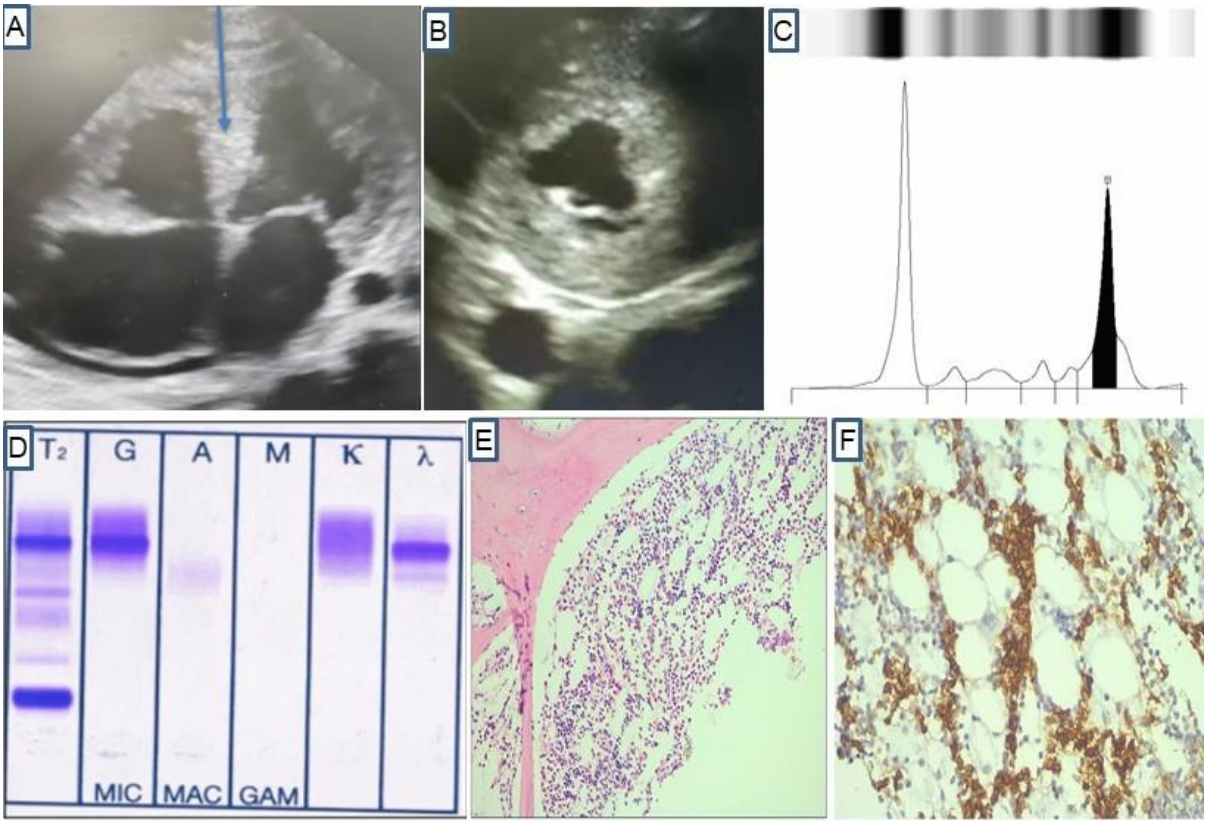

Figure 2: Transthoracic echocardiography, serum electrophoresis, and bone marrow biopsy findings are presented herein. (A) Two-dimensional echocardiography (apical 4-chamber view) depicts a sparkling septum (marked with an arrow), along with dilated right and left atria. (B) The parasternal short-axis view shows prominent left ventricular hypertrophy. (C) The serum protein profile on agarose gel electrophoresis demonstrates monoclonal gammopathy (M spike) in the gamma globulin region. (D) Immunofixation electrophoresis identifies the M spike as IgG lambda and its isomer as lambda. (E) The bone marrow biopsy (20x Hematoxylin and eosin staining) illustrates interstitially scattered plasma cells. (F) Immunohistochemistry for CD138 (40x) showcases interstitially prominent clusters of plasma cells.

Our patient presented with congestive heart failure. Given her postmenopausal status and advanced age, the initial differential diagnosis considered was ischemic cardiomyopathy. However, this was ruled out due to the absence of previous acute coronary syndrome events, no comorbidities such as diabetes, and the lack of regional wall motion abnormalities on 2D echocardiography. As the echocardiogram suggested RCMP with a sparkling septum, the primary differential diagnosis was cardiac amyloidosis. Other potential etiologies, such as hemochromatosis, hypereosinophilic syndrome (HES), endomyocardial fibrosis, and sarcoidosis, were excluded through normal differential leukocyte count, normal ferritin and transferrin saturation levels, normal serum angiotensin-converting enzyme levels, and the absence of history or examination findings indicative of sarcoidosis.

The patient was initially managed for congestive heart failure with diuretic therapy. After adequate decongestion, a β-blocker, spironolactone, and ramipril were introduced as part of the treatment regimen. Upon establishing the diagnosis of cardiac amyloidosis with multiple myeloma, the patient was initiated on chemotherapy in collaboration with a clinical hematologist. The treatment regimen consisted of bortezomib (2 mg) and cyclophosphamide (300 mg/m^2), known as the VC regimen. Concurrently, anti-HCV therapy was started using a combination of Sofosbuvir (400 mg)

and Daclatasvir (60 mg), which the patient tolerated well.

The patient's symptoms improved during her hospital stay, and she was discharged in a hemodynamically stable condition. Outpatient chemotherapy for cardiac amyloidosis was initiated, and she was advised to follow up for a cardiac MRI and Tc-99m pyrophosphate scan after optimizing heart failure and heart rate management with goal-directed medical therapy. Still, 2 weeks post-discharge, the patient suffered a sudden cardiac arrest at home.

DISCUSSION

AL amyloidosis is characterized by the deposition of proteins derived from immunoglobulin light chain fragments, often associated with monoclonal gammopathy of undetermined significance and multiple myeloma. Approximately 10% to 15% of patients with multiple myeloma may develop AL amyloidosis.[2] Cardiac amyloidosis is characterized by extracellular deposition of misfolded proteins in the heart.[3] It is the most common cause of RCMP, followed by cardiac sarcoidosis and hemochromatosis.[4] Cardiac amyloidosis primarily affects the ventricular myocardium and conduction system. However, in some cases, it may also involve the coronary vessels, pericardium, and endocardial valves. Typically, features of diastolic failure and right heart failure are predominant, but the condition can progress to biventricular failure and, in advanced stages, both systolic and diastolic failure. Notably, our patient presented with biventricular failure symptoms at onset, which is less commonly reported and underscores the importance of not overlooking biventricular failure in the elderly population. Cardiac AL amyloidosis is definitively diagnosed through cardiac biopsy. Nevertheless, for individuals with suspected AL amyloidosis, a less invasive diagnostic approach with relatively high sensitivity (~80%) involves the initial evaluation of amyloid using labial salivary gland biopsies, periumbilical fat aspirates, and bone marrow samples.[5] The diagnostic criterion for cardiac amyloidosis is the presence of amyloid deposits within endomyocardial biopsy samples. These deposits are stained with Congo red, exhibiting green birefringence under polarized light.[6, 7]

Approximately 45% of individuals with AL amyloidosis display a low-voltage QRS complex, while about 47% exhibit a pseudo-infarct pattern characterized by abnormal Q waves. This occurrence is more prevalent compared to patients with ATTR amyloidosis.[3] Unexplained enhanced cardiac wall thickness, without underlying causes such as uncontrolled hypertension, alongside increased ventricular wall thickness with greater echogenicity reminiscent of granular sparkling, can be observed in 2D echocardiography. This imaging modality also reveals a unique bull's eye appearance resulting from the LV strain pattern, where the apex is preserved.[4,6]

Although cardiac AL amyloidosis typically preserves LVEF, a subset of patients may experience reduced LVEF. Nuclear scans, such as 99mTc-pyrophosphate and 99m3,3-diphosphono-1,2-propanodicarboxylic acid, have proven useful in detecting ATTR amyloidosis.[8]

Patients with AL amyloidosis frequently develop length-dependent mixed sensory and motor peripheral neuropathy, as well as autonomic neuropathy. Autonomic neuropathy can result in orthostatic hypotension. While cranial neuropathies are rarely associated with AL amyloidosis, it remains an underdiagnosed cause of this condition. In a review of 12 cases of cranial nerve involvement associated with AL amyloidosis in existing literature, facial nerve paralysis was reported in 7 instances.[9,

[10] The remaining cases demonstrated the involvement of various cranial nerves, such as the olfactory, oculomotor, trochlear, trigeminal, abducens, and hypoglossal nerves. Our patient's development of facial nerve palsy during hospitalization further emphasizes the rapid progression of the disease and its poor prognosis in this case. High-dose melphalan followed by hematopoietic stem cell transplantation, resulting in hematological remission, is a reasonable treatment option for select patients.[11] For patients ineligible for hematopoietic stem cell transplantation, preferred regimens include melphalan and dexamethasone or cyclophosphamide, thalidomide, and dexamethasone.[12]

Despite advances in treatment, the limited life expectancy of patients with cardiac AL amyloidosis is likely due to delayed diagnosis and intervention. Without treatment, the condition invariably leads to death, with a life expectancy of less than 6 months.[5] Therefore, a high clinical suspicion, timely diagnosis, and prompt treatment are essential to improve patient outcomes. Despite initiating treatment early during hospitalization, the disease had already advanced significantly, with early cardiac involvement and severely impaired ventricular function, increasing the risk of sudden cardiac death. The absence of hematological or systemic symptoms of multiple myeloma, with the initial presentation of cardiac amyloidosis, makes this case rare and unique.

In conclusion, cardiac amyloidosis may be the presenting manifestation of a systemic disorder such as multiple myeloma. High clinical suspicion is essential for early diagnosis since it enables timely treatment, halts ongoing cardiac injury, and reduces the risk of sudden cardiac death. In research-limited settings, 2D echocardiography may be the only available diagnostic modality. AL amyloidosis can cause cranial neuropathy, with lower motor neuron-type seventh cranial nerve involvement being the most common presentation.

Conflict of Interest

None

REFERENCES

1. Merlini G, Palladini G. Differential diagnosis of monoclonal gammopathy of undetermined significance. Vol. 2012, Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program. 2012.

2. Kyle RA, Linos A, Beard CM, Linke RP, Gertz MA, Michael O'fallon W, et al. Incidence and Natural History of Primary Systemic Amyloidosis in Olmsted County. 1950.

3. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses: Disease profiles and clinical courses of the 3 main types. Circulation. 2009 Sep; 120(13):1203–12.

4. Grogan M, DIspenzieri A, Gertz MA. Light-chain cardiac amyloidosis: Strategies to promote early diagnosis and cardiac response. Vol. 103, Heart. BMJ Publishing Group; 2017. p. 1065–72.

5. Pellikka PA. Endomyocardial biopsy in 30 patients with primary amyloidosis and suspected cardiac involvement. Arch Intern Med. 1988; 148(3).

6. Arbustini E, Merlini G, Gavazzi A, Grasso M, Diegoli M, Fasani R, et al. Cardiac immunocyte-derived (AL) amyloidosis: An endomyocardial biopsy study in 11 patients. Am Heart J. 1995; 130(3 PART 1).

7. Ilias Basha H, Raj E, Bachuwa G. Cardiac amyloidosis masquerading as biventricular hypertrophy in a patient with multiple myeloma. Available from: http://casereports.bmj.com/

8. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. 99mTc-

pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging. 2013; 6(2).

9. Traynor AE, Gertz MA, Kyle RA. Cranial neuropathy associated with primary amyloidosis. Ann Neurol. 1991; 29(4).

10. Martins AM, Ferreira FS, Leite IM, Fonseca M, Victorino R. Facial Paralysis as Initial Manifestation of Light-chain Amyloidosis. Cureus. 2019 Aug 29;

11. Sanchorawala V, Wright DG, Seldin DC, Falk RH, Berk JL, Dember LM, et al. Low-dose continuous oral melphalan for the treatment of primary systemic (AL) amyloidosis. Br J Haematol. 2002; 117(4).

12. Wechalekar AD, Goodman HJB, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. Blood. 2007; 109(2).