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A Case Series on Patients of Cardiac Amyloidosis with Varying Initial Clinical Presentation in a Tertiary Health Care Cardiology Outpatient Service, Kerala

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Abstract

The study aims to assess the outcome of early diagnosis in cardiac amyloidosis and to emphasize the need for high clinical index of suspicion even before onset of cardiac symptoms. Recent advances in immunohistochemical markers, molecular and genetic studies carry early diagnostic and grave prognostic significance. This study concludes a significant inverse relationship between time of diagnosis after the onset of cardiac symptoms and percentage survival rate of the affected individuals.

Introduction

Cardiac Amyloidosis (CA) has emerged as an underdiagnosed cause of Heart Failure (HF) that is associated with significant morbidity and mortality, particularly in later stages of disease [1,2]. Heart failure with amyloidosis is associated with higher odds of in-hospital mortality, 30-day readmission, and a longer length of hospital stay. It may be the presenting feature of the disease or may be identified while investigating a patient presenting with other organ involvement.

Small, single-centric studies have estimated the prevalence of Cardiac Amyloidosis as 13% among patients with {HF with preserved ejection fraction} [3,4]. Most cases of Cardiac Amyloidosis are of either transthyretin type, which may be acquired in older individuals or inherited in younger patients, or acquired monoclonal immunoglobulin light chain (AL) type.

Significant advances in non-invasive diagnostic testing [5,6] and targeted amyloid therapeutics [7] have piqued clinical enthusiasm; however, diagnostic delays of up to 34 months still persist [8,9]. Amyloidosis being a systemic disorder, biopsies can be obtained from several sites, including the heart {in ATTR -transthyretin amyloidosis}, due to predominant cardiac involvement), abdominal fat pad, bone marrow (as part of work-up for plasma cell dyscrasia in suspected AL amyloidosis), or kidney [1]

Prognosis in amyloidosis depends predominantly on the degree of cardiac involvement. Atrial fibrillation is common and is assosiated with poor prognosis. Though the prognosis is better in ATTR amyloidosis, both types of amyloidosis carry a high risk of mortality. As a result, timely diagnosis is critical to allow treatment initiation in earlier stages of disease, where inhibition of amyloid fibril formation has greater clinical benefit. Treatment for amyloidosis has evolved significantly over the past several years [7]. Treatment follows two parallel paths:

A) Treating the consequence of organ dysfunction and attempting to slow the progression of disease with chemotherapy against the plasma cells.

B) Cardiac specific treatment including {diuretics/salt restriction} and managing arrhythmias.

Currently available therapies include transthyretin stabilizers and transthyretin synthesis inhibitors for transthyretin amyloidosis, chemotherapy and autologous stem cell transplantation for light chain amyloidosis, and cardiac transplantation for selected patients with advanced HF [10]. ACE-Inhibitors, Angiotensin Receptor Blockers and Beta blockers are poorly tolerated and may result in profound hypotension. Pacemakers are frequently required due to assosiated conduction disease .As the disease is irreversible with high mortality, a cardiac transplant may be considered in indicated patients.

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Table 1: One year follow up details of the patients included in the study.

Basic Characterstics	1	2	3	4	5	6	7	8
Age (years)	63 years	41 years	72 years	63 years	53 years	51 years	68 years	69 years
Gender	Female	Female	Male	Male	Female	Female	Male	Male
BMI (kg/m^2)	26.3	26	16	63	21	22	22	26
Comorbidities	Nil	Nil	CAD, COPD	CKD, CLD	DLP hypothyroidism	DM	Nil	Hypothyroidism Hypertension Dyslipidemia
Initial presentation	CCF	Arthralgia	weight loss	VT	CCF	weight loss, malaena	Difficulty in walking since 5years worsened in past 1 year.	Recurrent syncope, limb weakness and spasticity.
Other organ involvement	liver	Shoulder joint, liver	Lung- type 2 respiratory failure	Gastroparesis-antral ulcers	liver, spleen	Liver, chronic proctitis, chronic deodinitis	Hypotonia Sensori-motor axonal polyneuropathy gastric ulcer	Chronic Sensori-motor polyneuropathy-
Hemoglobin(g/dl)	10.2	11.8	13.4	10.4	13.2	11.4	15	12
Serum creatinine	0.8	0.9	1.2	2.7	4.4	0.9	0.7	1.2
NT proBNP	7096	553	5058	15,070	>25,000	4311	279	500
Troponin	0.26	negative	0.12.	0.14	0.8	0.05	negative	negative
DFLC (kappa -3.3-19) Lamda -5.7-26}	Kappa-6 Lamda-448	Kappa-6380 Lamda-9	Kappa-20 Lamda-874	Kappa-12 Lamda-4401	Kappa-20 Lamda-133	Kappa-1123 Lamda-35	Kappa-17.44 Lamda-12.61	Kappa-23 Lamda-12
Free Kappa / lamda ratio {0.26-1.65}	0.01	708	0.02	0.002	0.15	31.4	1.38	1.9
24- Hour Urine Protein (<150)	130	250	146	1785	5481	1689	NA	NA
Bone marrow plasma cells (% nucleated marrow cells)	39%	4%	2%	26%	4%	7%	2%	8%
Baseline LV function	60%	60%	55%	35%	40%	60%	60%	60%
Genetic study	Not done	Not done	Not done	Not done	Not done	Not done	TTR+ on exon 5 hetrozygous -heriditary amyloidosis {autosomal dominant}.	TTR+ on exon 5 hetrozygous -heriditary amyloidosis {autosomal dominant }. PMP22(-) Exon-5hetrozygous -heriditary amyloidosis {autosomal dominant}.
Time from onset of symptoms to diagnosis (months)	2 months	4 months	1 year	2 year	4 months	8 months	1 year	8 months
Treatment regimen (CyboR-D based chemotherapy)	Tolerated 12 cycles of chemotherapy	Chemotherapy followed by stem cell transplantation	Initiated on chemotherapy, but could not tolerate	Initiated on chemotherapy, But couldn't tolerate	Tolerated 12 cycles of chemotherapy	Initiated on chemotherapy	Intiated on chemotherapy	Tolerated 12cycles of chemotherapy
One year follow up details	On maintainance	On mainatainance	Cardiac arrest	Cardiac arrest	On maintenance	On maintenance	On maintainance	On mainatainance

Methods

The study was a retrospective study with one year follows up of the patients conducted in the department of cardiology, Rajagiri hospital. The study subjects included all patients who were diagnosed with cardiac amyloidosis in Rajagiri hospital from time period August 2020 to August 2021. The relevant cinical information were obtained from electronic case report of the patient. Cinical details that were collected included age, gender, BMI(kg/m^2), associated comorbidities, intial presenting symptoms and assessment of of liver, spleen and other organ involvement was done. The haemoglobin, serum creatinine, NT proBNP, 24 hour urine protein ratio, troponin, baseline LV function at the time of diagnosis was studied. Genetic study done by the patient was analasyed. Fat pad biopsy, immunohistochemistry slides of the patients available in department of pathology was studied for identifying the type of amyloidosis. The data was then entered in spread sheets of Microsoft Office Excel and the variables were compared quantitatively and qualitatively. The treatment details in relation to number of chemotherapy cycles [CyboR-D based chemotherapy), stem cell transplantation were collected from the department of hematology. The treatment follow of the patient was continued for a period of one year by simultaneously entering them in the spreadsheet and the results were tabularised as in (Table 1). These patients were furthur divided according to revised Mayo prognostic index 2012.

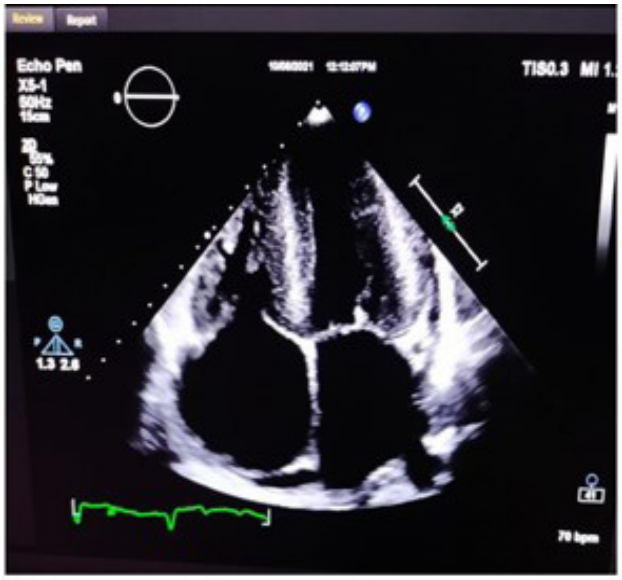

Figure 1: Echocardiogram of patient with cardiac amyloidosis showing biatrial enlargement.

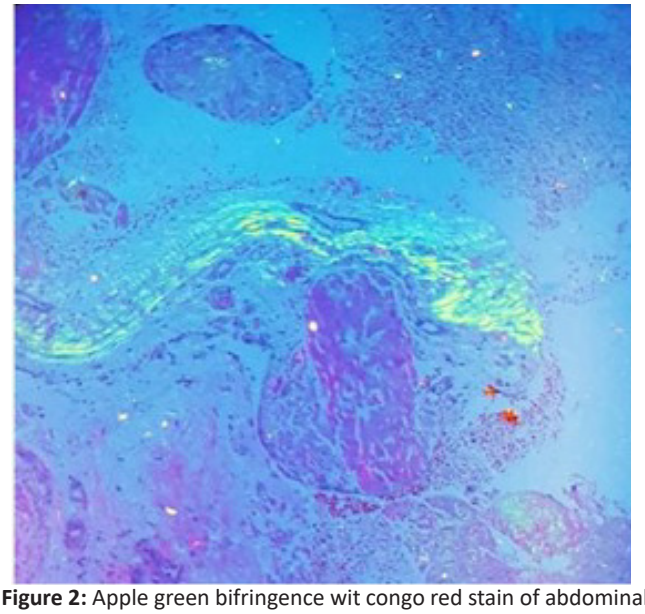

Figure 2: Apple green bifringence wit congo red stain of abdominal fat pad biopsy specimen.

Discussion

A total of 8 patients were included in the study. The predominant age group affected was 60-70 years with mean age group as 60 years. Cardiac involvement in amyloidosis presents commonly with arrhythmias and/or rapidly progressing heart failure or occasionally with polyneuropathy, arthralgia or gastrointestinal symptoms. Once a patient develops cardiac symptoms, they usually have large amount of amyloid in the heart. Amyloid deposit in the atrium causes an irregular surface that makes these patients prone to thrombus formation, irrespective of atrial fibrillation development. Amyloid fibrils cause stiffening of heart which explains restrictive physiology found on echocardiogram.

Genetic study encouraged early diagnosis. Patients diagnosed with short duration of symptoms had good prognosis even though they presented in heart failure. Meanwhile patients diagnosed with long duration of symptoms had poor prognosis even though they were not in failure. A better treatment outcome in seen in patients who had stem cell transplantation following chemotherapy. The patients with assosiated multiorgan failure couldn't tolerate chemotherapy and succumbed to death while the rest are on maintainance on one year follow up.

Thus we could see in our study, a significant inverse relationship between time of diagnosis after the onset of cardiac symptoms and their life expectancy rate and could conclude high clinical index of suspicion is needed for early diagnosis and good outcome.

Author Statements

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Conflict of Interest

None declared.

Informed Consent

Written informed consent was obtained from the patient.

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