Case Report

Infiltrative Cardiomyopathy Causing Heart Failure with Compromised Ejection Fraction (HFrEF) : An entity to look out for

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Infiltrative cardiomyopathy is characterized by deposition of abnormal substances within the heart tissue resulting in diastolic dysfunction and less commonly systolic dysfunction late stage of the disease. The more common types of infiltrative cardiomyopathy are cardiac amyloidosis, sarcoidosis and hemochromatosis. We present the case of a 73 year old male with dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea and fainting episodes. Electrocardiogram (ECG) showed low-voltage QRS complexes, Right Bundle Branch Block (RBBB) with associated Left Anterior Fascicular Block (LAFB) and on echocardiogram demonstrated reduced systolic function. The Cardiac MRI demonstrated restrictive cardiomyopathy with both systolic and diastolic dysfunction concluding that there is infiltrative cardiomyopathy due to either sarcoidosis or amyloidosis. Caution must be exercised while using the guideline medical therapeutic drugs that form the pillar of comprehensive heart failure therapy as they have many untoward side effects.

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Infiltrative cardiomyopathy is characterized by deposition of abnormal substances within the heart tissue resulting in diastolic dysfunction and less commonly systolic dysfunction late in the course of the disease[1]. The more common types of infiltrative cardiomyopathy are cardiac amyloidosis, sarcoidosis and hemochromatosis.

Amyloidosis describes the multisystem deposition of insoluble fibrillary proteins known as amyloid fibrils. Cardiac involvement is common and is a major cause of morbidity and mortality in patients with amyloidosis[2]. Cardiac involvement occurs in about 50% of Amyloid Light Chain (AL) cases, the most aggressive form resulting from an underlying plasma cell dyscrasia and has poor prognosis[3]. Hereditary Transthyretin-derived (ATTR) is an autosomal dominant condition classically manifests in the sixth decade of life, causes neuropathy and cardiomyopathy and is frequently misdiagnosed as hypertensive cardiomyopathy[4,5]. The heart is rarely involved in amyloidosis stemming from chronic inflammation such as secondary (AA) amyloidosis[6]. Senile Systemic Amyloidosis (SSA) is similar to ATTR in its course[7].

Cardiac deposition of amyloid fibrils affects cardiac contractility, conduction and coronary blood flow resulting in progressive biventricular diastolic dysfunction with or without systolic dysfunction, heart block, ventricular arrhythmias and myocardial ischemia[1]. The main manifestation of amyloid cardiomyopathy is clinical heart failure[8]. Syncope and Presyncope, high-grade conduction disease and thromboembolism from atrial fibrillation[9-11] are also known.

Editor's Comment :

- When we deal with infiltrative cardiomyopathy, possibility of amyloid ethiology should be there at the back of our mind. Low-voltage QRS (all limb leads <5 mm in height) in conjunction with other abnormalities of conduction is pathognomonic of cardiac amyloid. Even though gold standard for diagnosis of cardiac amyloidosis is endo myocardial biopsy., ECG, echo and CMR in conjunction with tissues from other organs like abdominal fat pad (fine needle aspirate), rectum or kidney staining positive for amyloid will confirm the diagnosis.

Case Report

This case report of a 73-year-old retired security officer who presented to the cardiac clinic with dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, abdominal swelling and pain, dizziness, fainting episodes, low BPs and soft tissue injury to the left leg following a fall. He had been on Torsemide 10mg OD, losartan 50mg OD, Bisoprolol 5mg OD, Spironolactone 25mg OD and Ivabradine 7.5mg od without improvement. He neither smoked nor consumed alcohol. He has slightly lower blood pressure (95/58mmHg) with a bradycardia of 53bpm. He had a regular pulse with elevated internal jugular venous pressures, loud heart sounds with pan systolic murmurs loudest at the apex, tender

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hepatomegaly and a grade 3 edema. His labs showed elevated creatinine of 237µmol/l (60-130), uric acid 728 mmol/l (202-416), mild hypochromic microcytic anemia of 11.5g/dl [Mean Corpuscular Volume (MCV)=91, Mean Corpuscular Hemoglobin (MCH)=25, Mean Corpuscular Hemoglobin Concentration (MCHC)=27]. HbA1c and TSH were normal. Left foot X-rays had shown weber B1 lateral malleolar fracture with a non-displaced fracture of the base of the proximal phalanx of the first toe. Losartan and bisoprolol doses were reduced due to low BP.

The patient had some improvement though when he presented to the clinic three months later. He had dyspnea NYHA class 2 with bilateral pedal edema and a lack of coordination. There was no orthopnea or Paroxysmal Nocturnal Dyspnea (PND). He had a normal coronary angiogram. An ultrasound showed acute focal small bowel inflammatory disease; CT Abdomen (CTA) with IV and oral enhancement be undertaken for correlation. He also had mild bilateral scrotal hydrocele. His creatinine improved to an average of 180µmol/l and his hemoglobin had gone up to 13.2g/dl. He was put on Sacubitril&Valsartan 100mg PO OD, Bisoprolol 10mg PO OD, Eplerenone 25mg PO OD and Torsemide 20 mg PO OD. Phosphorus and calcium levels were normal, H pylori was negative.

Two months later, his hemoglobin had gone to 14.3g/dl, but the creatinine had gone up to 223µmol/l. The Electrocardiograms (ECG) had consistent features of low-voltage QRS complexes, Right Bundle Branch Block (RBBB) with associated Left Anterior Fascicular Block (LAFB); echocardiogram had consistently shown reduced systolic function with a Left Ventricular Ejection Fraction (LVEF) of 31%. Cardiac MRI (CMR) showed a patient in heart failure with an ejection fraction of 24% features of systolic and diastolic dysfunction and features of a restrictive cardiomyopathy. Provisional diagnosis of cardiac sarcoidosis / cardiac amyloidosis (ATTR-amyloidosis) were considered (Figs 1&2).

Discussion

Clinical features of heart failure is the main manifestation of amyloid cardiomyopathy. Presyncope, syncope and conduction disease manifesting as RBBB and LAFB are also associated features. Extra-cardiac manifestation Chronic Kidney Disease (CKD), neuropathy, hypothyroidism and possible gastrointestinal disease manifesting with iron deficiency anemia possibly from gastrointestinal bleeding are also known to occur.

Low-voltage QRS (all limb leads <5 mm in height) is pathognomonic of cardiac amyloid[12]. This tends to occur with other abnormalities of conduction like 1st, 2nd, or 3rd degree Atrioventricular (AV) block and nonspecific intraventricular conduction delay. Atrial fibrillation, atrial flutter and ventricular arrhythmias may occur rarely[12]. The low voltage QRS complexes and the conduction abnormalities were a strong hint to the underlying pathology causing the patients symptoms.

On echocardiogram,biventricular wall hypertrophy, normal or reduced LV size, preserved ejection fraction, bi-atrial enlargement and progressively worsening diastolic dysfunction toward a restrictive pattern are the hallmarks of amyloid cardiomyopathy[13]. This is also good for monitoring disease progression[1]. Pericardial effusion and thickening of valves and papillary muscles are commonly found in echo. Reduced cardiac output points to a disease in its late stage. Low-voltage QRS on ECG combined with LVH on echo is very suggestive of cardiac amyloid[12].

Global transmural or subendocardial Late Gadolinium Enhancement (LGE) is the classical finding on CMR[14] The CMR of our patient indicated transmural LGE involving the basal LV and extending into the RV with areas of subendocardial sparing at the RV free wall; subepicardial and mid wall LGE in the mid cavity LV with sparing of segment 7 (anterior); and subepicardial in mid wall LGE at the apex with sparing of segment 13

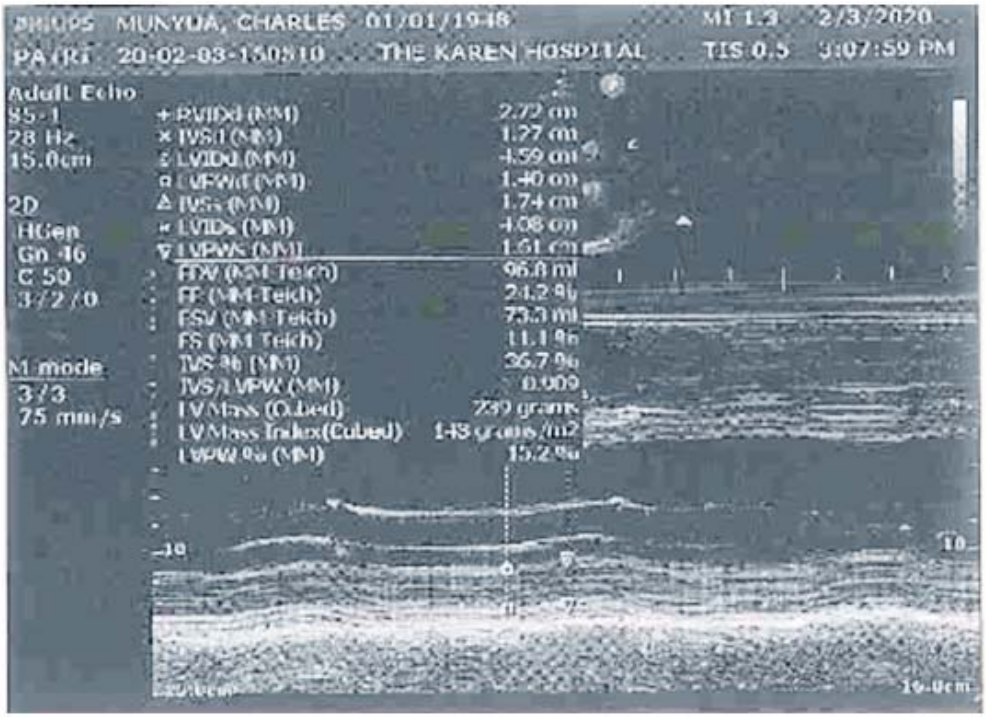

Fig 1 — Echocardiogram depicting reduced ejection fraction

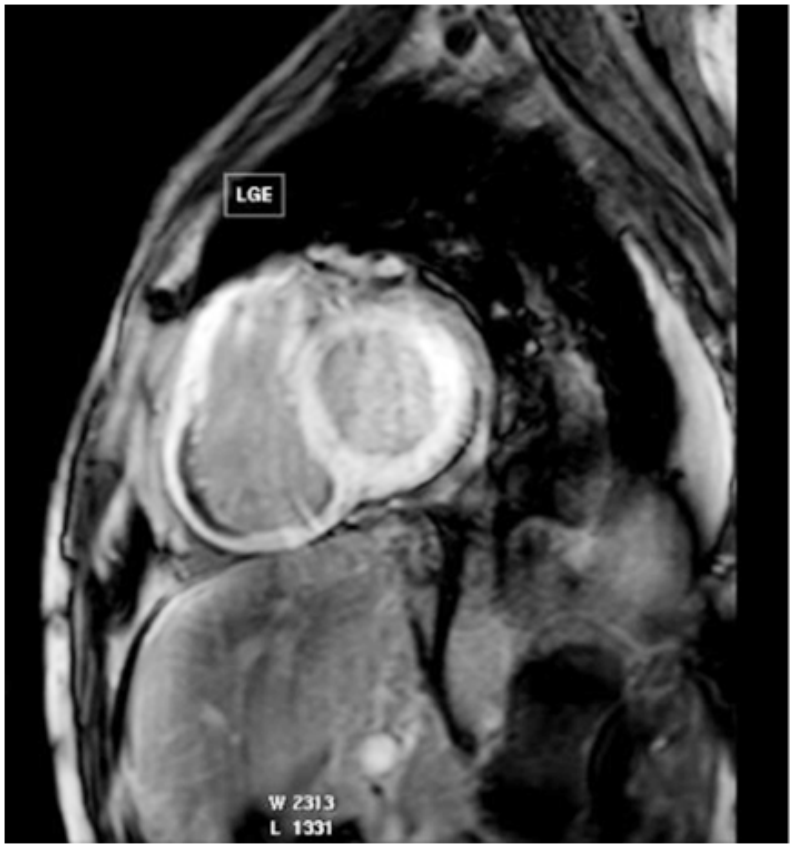

Fig 2 — Cardiac MRI illustrating late gandolium enhancement involving left and right ventricle

(anterior), thus making a strong case for cardiac amyloidosis.

The gold standard for diagnosis of cardiac amyloidosis is endomyocardial biopsy. However, features suggestive of cardiac amyloid on ECG, echo and CMRI in conjunction with tissues from other organs like abdominal fat pad (fine needle aspirate), rectum or kidney staining positive for amyloid affirms the diagnosis of cardiac amyloid[1]. The suspicion of AL amyloidosis warrants additional investigations: a bone marrow biopsy to evaluate the underlying plasma cell dyscrasia and serum and/or urine protein electrophoresis[1].

The major differential diagnosis of cardiac amyloidosis is cardiac sarcoidosis, a condition in which noncaseating granulomas, a pathological feature of sarcoidosis, form in the cardiac tissue leading to progressive heart failure and Sudden Cardiac Death (SCD). Cardiac involvement only occurs in 5% of people with sarcoidosis, whose peak incidence is in the ages between 25-45 years, marking a major difference from cardiac amyloidosis demographics[15]. Tissue edema in the early stages cause myocardium thickening and diastolic dysfunction whereas in the latter phase of fibrosis the ventricles dilate, hypokinesia ensue and systolic dysfunction predominates. It can also result in conduction system abnormalities including reentrant arrhythmias[16].

Patients with cardiac sarcoidosis usually present with asymptomatic electrocardiographic findings, heart failure and Sudden Cardiac Death (SCD) from complete heart block or ventricular tachyarrhythmia's, manifesting as palpitations or syncope[1]. CMR and Positron Emission Tomography (PET) scan are techniques of choice in cardiac sarcoidosis workup in addition to ECG and echo[17]. Pacemakers and Implantable Cardioverter-defibrillators (ICD) to prevent SCD, with steroids and/or immuno-suppressive agents is the standard of care[17]

Similar infiltrative cardiomyopathies are hemo-chromatosis and iron overload cardiomyopathy, Fabry disease, Danon disease and Friedreich's ataxia[1].

Cardiac amyloidosis treatment is two-pronged: managing heart failure and targeted therapy for underlying protein disorder. Judicious use of diuretics and avoidance of betablockers and ACE-inhibitors to avert profound hypotension due to over-diuresis and autonomic neuropathy is advised[18,19]. Maintenance of adequate filling pressures and the heart rate are vital because of the restrictive pathophysiology. If not careful, the medication may lead hypotension and progressive worsening of renal function. The medication has to be titrated for achieving optimal outcomes in these patients.

Chemotherapy, and rarely cardiac transplant is indicated for AL amyloidosis[20]. In ATTR liver transplantation is potentially curative if performed before cardiac involvement[21]. Pharmacotherapies designed to reduce, stabilize or silence the autosomal dominant amyloidosis activity (ATTR) are under active investigation and include Non-steroidal Anti-inflammatory Drugs (NSAIDs) Diflunisal and its non-NSAID analog Tafamidis[22]. Our patient should volunteer for enrolment in these ongoing studies to further elucidate the importance of these novel drugs in cardiac amyloidosis more so to people of African descent.

Conclusion

Cardiac amyloidosis is challenging to diagnose and to treat. Clinical features in addition to concentric LVH on echocardiography in the presence of low voltage QRSs in the limb leads on ECG are highly suggestive. CMR is quite important in increasing the probability of amyloidosis as well as ruling out other differential diagnosis even in the elderly persons. Caution must be exercised while using the guideline medical therapeutic drugs that form the pillar of comprehensive heart failure therapy as they have many untoward side effects.

Advanced cases of cardiac amyloidosis, cardiac transplantation is an indication.Patient stable on follow up and awaiting further evaluation to confirm diagnosis.

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