Abstract:
Cardiac amyloidosis is a rare condition. Many cases of progressive heart failure due to cardiac amyloidosis remain undiagnosed, because of the rarity and lack of suspicion. Cardiac deposition, leading to infiltrative cardiomyopathy, is a common feature of amyloidosis. Cardiac amyloidosis should be considered in patient with clinical features of congestive cardiac failure, preserved ventricular systolic function and a discrepancy between a low QRS voltage on electrocardiography, apparent ventricular hypertrophy and increased echogenecity on echocardiogram. Treatment options are limited and patients are also poor responders in late stages. Hence the need for a high index of suspicion, appropriate investigations, early diagnosis and recent advances in therapy which can, when appropriately used, significantly improve patient quality of life and survival.

Keyword: Amyloidosis, cardiac amyloidosis, amyloid heart disease, endomyocardial biopsy, cardiac MRI.
The differentiation of the types of cardiac amyloidosis is not always straightforward. We present here a case of histopathologically proven cardiac amyloidosis, in a forty-two-year-old male, with symptoms of congestive cardiac failure, who was referred to our centre with the diagnosis of hypertrophic cardiomyopathy and mild pericardial effusion. We discuss the electrocardiogram, echocardiography, cardiac catheterization, cardiac MRI and endomyocardial biopsy pictures seen in case of cardiac amyloidosis along with prognosis and treatment.

**CASE DESCRIPTION:**
A forty-two-year-old male patient presented with complaints of progressively worsening dyspnoea with exertion, easy fatigability and decreased appetite for last six months duration. He was not a diabetic or hypertensive and had no addictions. He was diagnosed elsewhere as a case of hypertrophic cardiomyopathy with mild pericardial effusion. He had no family history of cardio-vascular disease, sudden cardiac death or syncope. He had no past history of chest pain or palpitations. On physical examinations he had average build and nutrition, afebrile, with a blood pressure of 108/70 mmHg and a heart rate of 72 beats per minute. He was breathing at a rate of 28 breaths per minute and his oxygen saturation on room air was 97%. When he stood, no significant orthostatic changes in blood pressure and heart rate were noted. Cardiovascular system examination revealed a regular rate and rhythm with an audible left ventricular fourth heart sound, a second heart sound with an increased intensity of the pulmonic component. Jugular venous pressure was not raised and pedal edema was absent, positive hepatojugular reflux was present. On respiratory system examination he had bilaterally equal air entry and normal vesicular breath sounds.

Laboratory values on admission are shown in Table 1. Haemogram, renal functions and thyroid profile were within normal limits.

**Table 1. Admission Laboratory Values**
Fig-1 Electrocardiogram revealed sinus rhythm, left ventricular hypertrophy with strain pattern and poor progression of R wave in leads V1 to V3.

Fig-2 Chest X-ray showed normal cardiothoracic ratio and bilaterally clear lung fields.
Table 1. Admission Laboratory Values

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Admission laboratory values</th>
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<tbody>
<tr>
<td>Glucose Fasting</td>
<td>122 mg/dL</td>
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<tr>
<td>Glucose 2 Hrs, Post Food</td>
<td>173 mg/dL</td>
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<tr>
<td>Haemoglobin</td>
<td>13.5 gm/%</td>
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<tr>
<td>Serum Urea</td>
<td>33 mg/%</td>
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<tr>
<td>Serum Creatinine</td>
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<td>Serum Sodium</td>
<td>138 mmol/L</td>
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<tr>
<td>Serum Potassium</td>
<td>4.2 mmol/L</td>
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<tr>
<td>Urine Protein (24 hours)</td>
<td>389 mg/Per day</td>
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<tr>
<td>ESR</td>
<td>8 mm</td>
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<tr>
<td>Lipid Profile</td>
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<tr>
<td>Total Cholesterol</td>
<td>127 mg %</td>
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<td>Serum Triglyceride</td>
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<td>HDL – Cholesterol</td>
<td>36 mg %</td>
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<td>LDL – Cholesterol</td>
<td>85 mg%</td>
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<tr>
<td>Serum Uric Acid</td>
<td>9.2 mg %</td>
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<tr>
<td>TSH</td>
<td>1.232 ( \mu )IU/ml</td>
</tr>
<tr>
<td>NT-Pro-BNP</td>
<td>0.35 pg/ml</td>
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Two-dimensional transthoracic echocardiogram revealed gross bi-ventricular hypertrophy, small intracavitatory chamber dimensions, and a granular “Sparkling” texture. Bi-atrial enlargement was noticed with thickened inter-atrial septum. The mitral and tricuspid valves were mildly thickened. Fig-3 (A) (B)
Transthoracic echocardiography images (A) – Apical 4-chamber view showing bi-ventricular hypertrophy, small intracavitatory dimensions and mild bi-atrial enlargement. (B) – Parasternal long-axis view showing concentric left ventricular thickening with pericardial effusion and increased echogenicity of myocardium. Transmitral pulse Doppler showed a restrictive filling pattern with an ‘E’ wave equal to 1.4 m/s and ‘A’ wave, equal to 0.6 m/s, and an E/A ratio of >2; reduced deceleration time 140 milliseconds and the diastolic wave of pulmonary vein flow higher than the systolic wave. Left-ventricular systolic function was normal (LV ejection function = 60%). In contrast LV diastolic dysfunction was noticed, as evidenced by severely diminished peak early diastolic velocity (E') of the medial mitral annulus on tissue doppler imaging. Blood velocity pattern at the mitral leaflet tips and in the pulmonary veins was reflective of elevated left atrial pressure. Hepatic vein Doppler study showed significant reversal of blood flow in inspiration. Mild pericardial effusion was also seen. Cardiac MRI showed concentric biventricular, biatrial wall and interatrial septal hypertrophy. In the time of inversion sequence the myocardium had shorter TOI value than the blood, hence myocardium (myocrit) nulled before the blood (Hematocrit). Diffuse subendocardial global hyperenhancement was noted in both the ventricles because of amyloid infiltration which stored gadolinium. Mild to moderate amount of pericardial effusion was reported. No pleural effusion or ascites was noted.
Cardiac MRI images: (A) – Horizontal long axis view showing concentric hypertrophy of both ventricles, thickened inter-atrial septum and pericardial effusion. (B) – Short axis view myocardium showing shorter TI value of 110 and nulled before blood. (C) – Short axis view showing blood nulled at larger TI value of 442. Bone marrow biopsy was done which showed mildly hypercellular marrow with trilineage hematopoiesis with mild eosinophilia and no specific lesion.

He underwent coronary angiogram and cardiac catheterization study followed by transjugular endomyocardial biopsy which revealed normal epicardial coronary arteries, normal LV and RV systolic function. Right heart catheterization had the following findings, mean right atrial pressure 4 mmHg, right ventricular pressure 35/6/15 mmHg, pulmonary artery pressure 29/13/20 mmHg and mean capillary wedge pressure of 14mm and difference of LVEDP-RVEDP of 8 mmHg present. Fig-5-Cardiac catheterization - Simultaneous right and left ventricular pressure tracing.

A transjugular endomyocardial biopsy was taken using Cook flexible biopsy forceps, tissue from multiple places were taken on the RV side of the interventricular septum. Histopathological report showed bundles of atrophied cardiac muscles surrounded by pale amorphous eosinophilic material which shows apple green birefringence on Congo red stain. Thioflavin T staining showed yellowish fluorescence.

DISCUSSION AND GENERAL REVIEW - AMYLOID HEART DISEASE:
Amyloid usually involves more than one organ system. Cardiac amyloidosis is a manifestation of one of several systemic diseases known as the amyloidoses. If a diagnosis of extra cardiac
amyloidosis has already been made, cardiac symptoms are readily attributable to cardiac amyloidosis. Diagnosis of cardiac or multiorgan amyloidosis is often not entertained until late in the course of the disease. Disease progression rate is different in various types of systemic amyloidosis, but in all cases presence and severity of cardiac involvement is the main deciding factors of prognosis. Cardiac amyloidosis is a myocardial disease in which extra cellular amyloid infiltration is seen throughout the heart. Amyloid deposits involve the ventricles and atria as well as perivascularly (particularly in the small vessels) and in the valves. The amyloid infiltrative process causes biventricular wall thickening with nondilated ventricles. Increased pressure in the thin-walled atria is associated with atrial dilation, despite thickening of the atrial wall by amyloid deposition.

CLINICAL FEATURES:
Various forms of cardiac amyloidosis commonly present with features of congestive heart failure, associated with nondilated left ventricle, with thickened walls and normal or mildly reduced left ventricular ejection fraction. A common presenting feature of amyloid heart disease is severe right-sided heart failure. In advanced disease profound peripheral edema and ascites is seen. Weight loss is a common finding and represents the effect of systemic disease or may be result of cardiac cachexia.

Amyloid heart disease may present as chest discomfort which is usually of atypical character, but typical angina, can occur because of involvement of the small vessels of the heart. Epicardial coronary arteries are normal on coronary angiogram, but imaging studies may be positive, myocardial flow reserve in such patients is impaired.

Small and persistent elevation of serum troponin is noticed which represents ongoing myocyte necrosis and it has been shown to be a negative prognostic factor. Although sudden death is common in AL amyloidosis, ventricular arrhythmias are an uncommon presenting feature. Dermatological manifestations such as easy bruising and periorbital purpura may occur. Stiffening and enlargement of the tongue (macrologosia), often with tooth indentation is seen in 10-20% of patients and sometime produces dysphonia and dysgeusia, change in voice specially hoarseness toward the end of the day probably represents the vocal cord involvement. Carpel tunnel syndrome and peripheral and autonomic neuropathy are common neurological symptoms. Right upper quadrant discomfort may be due to hepatic congestion or with amyloid hepatic infiltration.

Cardiovascular physical examination in amyloid heart disease patients with heart failure reveals sinus rhythm with normal to low radial volume pulse. Atrial arrhythmia (atrial fibrillation) is seen in 10 to 15% of the patients. The jugular venous pressure is often markedly elevated and prominent X and Y descents are noted. A left ventricular 3rd heart sound is rarely heard but in advanced cases a right ventricular third heart sound, which is associated with right ventricular dilatation and dysfunction. A fourth heart sound is almost never present possibly because of atrial dysfunction due to amyloid infiltration. Postural drop in blood pressure is seen particularly if autonomic neuropathy is present. Splenomegaly is rare but hepatomegaly is common and is due to either congestion from right heart failure or due to amyloid infiltration.
NON INVASIVE EVALUATION OF CARDIAC AMYLOIDOSIS

ECG: Characteristic electrocardiographic features include low voltage on the ECG (QRS Voltage amplitude 0.5mV in all limb leads or 1 mV in all precordial leads) or loss of anterior forces consistent with anteroseptal infarction. Rahman et al\textsuperscript{26} noted low ECG voltage in 56% and pseudo infarction pattern in 60% of cardiac amyloid patients. Atrial fibrillation and flutter are the most common arrhythmia and are present in 25% of patients with cardiac amyloidosis. Low voltage in ECG and interventricular septal thickness >1.98cm. on echocardiography made diagnosis of cardiac amyloidosis with a sensitivity of 72% and specificity of 91% \textsuperscript{27}.

ECHOCARDIOGRAPHIC FEATURES
Echocardiographic features of cardiac amyloidosis are distinctive. Common echo features are nondilated ventricles, with concentric left ventricular and right ventricular thickening prominent valves and infiltration of inter-atrial septum. Abnormal myocardial texture was noted and described as “granular sparkling”\textsuperscript{26,29} or “snow storm” appearance. In 5% of patients in the cardiac amyloidosis, Left ventricular infiltration may mimic HCM on echocardiogram\textsuperscript{30}. Other features of cardiac amyloidosis include thickened valve, and small pericardial effusions are documented in 40% of patients \textsuperscript{31}. Doppler echocardiography is useful in the diagnosis of cardiac amyloidosis. Advanced disease showed restrictive transmitral flow pattern, short deceleration time of the ‘E’ wave and a low velocity of ‘A’ wave with associated abnormality in pulmonary venous flow. Doppler features depend upon the stage of the disease progression and advanced diastolic dysfunction noted as myocardial infiltration progresses\textsuperscript{32}. Tissue Doppler and strain and strain rate imaging give valuable information for evaluating the prognoses in cardiac amyloidosis \textsuperscript{33}.

In summary there are many echocardiographic features seen in amyloidosis, but the most sensitive and specific test for detecting cardiac amyloidosis is a low ECG voltage-to-ventricular mass ratio \textsuperscript{34}.

Cardiac MRI:
Cardiac MRI is useful in the diagnosis of amyloidosis if echocardiographic features are suspicious \textsuperscript{35}. Studies done in the past showed that cardiac MRI has a role in discriminating between hypertrophic and restrictive cardiomyopathy. The presence of late gadolinium enhancement is a characteristic feature of cardiac amyloidosis \textsuperscript{36}. Recent studies of cardiac MRI on advanced amyloid heart disease showed an unusual pattern characteristic by global subendocardial late gadolinium enhancement and associated abnormal myocardial and blood gadolinium kinetics.

Radiolabelled serum amyloid P component (SAP) – Scintigraphy:
Serum amyloid P component is an invariant plasma glycoprotein of the pentraxin family that became highly concentrated in any type of amyloid deposit due to its calcium dependent, binding to all types of amyloid fibrils. Radio labeled SAP on intravenous injection distributes between the circulating and the amyloid bound SAP pools in proportion to their size and than be imaged and quantified \textsuperscript{37}. It is a simple, reproducible method of quantifying the uptake of 123-I-labeled serum amyloid into vascular organs. It’s commonly used as a diagnostic tool of AL and AA amyloidosis and less for ATTR-type amyloidosis \textsuperscript{38}.

Biochemistry: In amyloid heart disease, cardiac biomarkers are elevated,
often to a degree that seems to be disproportionate to the symptoms of congestive heart failure. **NT-Pro-BNP**

**Elevated N-terminal pro-brain natriuretic peptide (NT-Pro-BNP)** is associated with many cardiac conditions. A very high level of NT-pro-BNP is consistent with cardiac amyloidosis and related to increased mortality\(^\text{39}\). Elevation of NT-Pro-BNP in AL amyloidosis is mainly because of direct toxic effect of the circulating amyloidogenic light chain. Increased ventricular filling pressure and amyloid infiltration. It’s helpful in identifying the presence of cardiac involvement in patients who don’t have a clear cut echocardiographic features.

**Troponin:**
Cardiac Troponin T and I are very sensitive biomarkers of myocardial injury. In amyloid heart disease amyloid deposition in the coronary microvasculature and compression of myocyte by amyloid infiltration causes troponin elevation. NT-Pro-BNP and troponin level in patients of cardiac amyloidosis at diagnosis provide prognostic information in amyloidosis and have been suggested as a method for staging the disease\(^\text{40}\).

**Cardiac Catheterization:**
Cardiac Catheterization give useful information other than to obtain endomyocardial biopsy, hemodynamic assessment and to look for coronary anatomy, in patients of amyloid heart disease. Advanced amyloid heart disease patients shows an elevated LVEDP, and the pressure tracing reveals dip-and-plateau pattern on waveform. Unlike constrictive pericarditis, amyloidosis is associated with LVEDP that exceeds RVEDP by at least 7 mmHg\(^\text{41}\). A pulmonary artery systolic pressure > 50 mmHg may occur in cardiac amyloidosis.

**Tissue Diagnosis:**
To establish a final diagnosis of amyloid heart disease requires a tissue biopsy which shows apple-green birefringence when stained with congo red and viewed under a polarizing microscope. Sulfated Alcian blue is an alternate stain with a high specificity for amyloid. Histological diagnosis can be made from other tissues also. FNAC of the abdominal fat is a simple procedure that is positive for amyloid deposition in > 70% of patients with AL type of amyloidosis. Endomyocardial biopsy is safe and simple procedure in skilled hands and its sensitivity is about 100% because the amyloid is widely deposited throughout the heart\(^\text{42}\). After establishing the tissue diagnosis of amyloid, search for plasma cell dyscrasia is required to confirm the diagnosis of AL amyloid. The combinations of an abdominal kappa and lambda ratio and a positive serum immunofixation made a diagnosis in 99% of patients with amyloidosis. Bone marrow biopsy is required to exclude myeloma and other rare disorder that can be associated with AL amyloidosis.

**AL Amyloidosis:**
It is the most commonly diagnosed form of the cardiac amyloidosis, AL Amyloidosis is a plasma cell dyscrasia, in which circulating amyloidogenic light than interact in the heart with constituents of the cell membrane and other local matrix components. Myocardial damage is due to deposition of extracellular amyloid and direct cell toxicity due to light chain oligomers. Cardiac AL amyloidosis patients have worse prognosis than patients with transthyretin amyloidosis.
Natural history of AL Amyloidosis is rapidly progressive and 80% mortality noted in 2 years\(^4^3\). The prognosis is particularly poor if heart failure is present with a median survival of 4 to 6 months. A staging system using NT-Pro-BNP and troponin of value in selection of AL amyloid patients who have a suitable risk for high-dose chemotherapy and autologous stem cell transplant.

**Treatment of AL Cardiac Amyloidosis:**
AL cardiac amyloidosis management focused on treatment of the heart failure and the treatment of the understanding plasma cell dyscrasias. Heart failure due to AL Amyloidosis usually responds poorly to conventional therapies. Optimal diuretics and salt restriction are the mainstay of management. Calcium channel blocker use is often associated with worsening of heart failure. No evidence of beneficial effect of beta blocker and ACE inhibitor seen in this group of patients. For patients in atrial fibrillation cautious use of digoxin is advisable but the risk of digoxin toxicity is high due to abnormal binding of drug to amyloid fibrin. Treatment of plasma cell dyscrasia requires chemotherapy for abolishing or at least significantly reducing the production of the amyloidogenic monoclonal light chains. Response to chemotherapy as evidenced by resolution of light chain production is associated with a reduction of serum NT-Pro-BNP and improvement in survival\(^4^4\). High dose chemotherapy with melphalan and other regimen using thalidomide, lenidomide and bortezomib with or without steroid supported by autologous, stem cell transplantation has been used in patients with AL amyloidosis. Heart transplantation followed by autologous stem cell transplantation has been reported in a small group of patients. To prevent sudden cardiac death in patients with AL Amyloidosis, implantable cardioverter-defibrillator (ICD) placement should be limited in patients with documented malignant arrhythmia.

**HEREDITARY AMYLOIDOSIS:**
This type of amyloid heart disease is usually associated with mutations in the gene for plasma protein transthyretin (TTR)\(^4^5\) and are labeled as (ATTR). Transthyretin contains 125 pairs of amino acid and about 100 different amyloidogenic missence point mutations have been described. The sex distribution is almost equal in hereditary amyloidosis. In contrast to a slight male preponderance in AL amyloid with cardiac involvement. Clinical presentation is of neuropathy, cardiomyopathy or combination of both. MacroGLOSSIA is usually not seen in ATTR. But carpal tunnel syndrome may be an early indicator of the disease. The most common transthyretin mutation seen in hereditary amyloidosis is the substitution of isoleucine for valine at position 122, which is seen in approximately 4% of the black population in united states\(^4^6\). Variants of apolipoprotein-A1 and gelsolin type can also cause cardiac amyloidosis and gelsolin cardiac amyloid is usually related to conduction system disease\(^4^7\) and may require permanent cardiac pacemaker.

**Management of Hereditary amyloid heart disease:**
Hereditary cardiac amyloidosis have a more indolent course and congestive cardiac failure is generally easier to manage\(^4^8\). ACE inhibitors and low dose beta blocker are tolerated in the absence of autonomic neuropathy. The only specific treatment for the transthyretin, fibrinogen and apo lipoprotein amyloidosis is organ-transplantation. Orthostatic liver transplantation is commonly performed for TTR associated familial amyloidosis.
Senile Systemic Amyloidosis:
Senile cardiac Amyloidosis (SCA) is the main clinical manifestation of senile systemic amyloidosis. It’s due to cardiac deposition of amyloid derived from the wild-type transthyretin (transthyretin with normal amino acid constitently) and most commonly presents as congestive heart failure. SCA shares predilection for men. The disease is rare before 70 years of age and median survival from the onset of heart failure is 7.5 years compared with about 1 year in patients with AL amyloidosis. The diagnosis should be suspected in an elderly man with unexpected right sided or biventricular heart failure and an echocardiogram showing left ventricular thickening with normal ventricular cavity size. There is no specific treatment for SCA, but patients with SCA often tolerate ACE inhibitor but the mainstay of therapy is still the judicious use of diuretics.

Secondary (AA) Amyloidosis:
It is a rare complication in chronic inflammatory disorder. The fibrils are derived from the acute phase reactant SAA. It is now uncommon in developed world due to eradication of the chronic infection. It’s occasionally seen in juvenile or adult rheumatoid arthritis and other rheumatic disorder like ankylosing spondylitis, and inflammatory bowel disease. Cardiac AA amyloid is very rare and is seen in only 2% of cases. Treatment focused upon suppressing the underlying disease.

Isolated Atrial Amyloidosis:
Isolated atrial amyloid (IAA) is a disease of elderly age group, with a female preponderance. Atrial natriuretic peptide (ANP) is produced locally in atrial myocytes and deposited within the atria as amyloid. IAA first appears in the third to fourth decade and it’s prevalence increases by approximately 15% every subsequent decade, by reaching almost 95% at age of 90 years. IAA diagnosis can only be made by histopathological examination of biopsy or autopsy material. Treatment of associated atrial arrhythmia is the mainstay of therapy.

Conclusion:
Cardiac amyloidosis, although uncommon, is characterized by typical appearance on echocardiography, the recognition of which alerts the clinician to make the probable diagnosis. Clinical awareness of the disease and a high index of clinical suspicion are important for early diagnosis, but unfortunately many cases are diagnosed late in the disease. Treatment and prognosis of individual form of amyloidosis differ greatly from each other. In AL amyloidosis severe cardiac involvement precludes high dose chemotherapy but if infiltration is limited to the heart, combined heart transplantation and chemotherapy offer a long term survival. Options for therapy of cardiac amyloidosis have now expanded. A high index of suspicion for the disease and early diagnosis with precise typing of amyloid deposit are critical to improved the outcome. Early referral to a centre specializing in the disease is of great value for the confirmation of diagnosis and treatment of this uncommon, but now potentially treatable disease.

References:


33. Perugini E., Rapezzi C., Piva T.; et al. Non-invasive evaluation of the myocardial substrate of cardiac amyloidosis by gadolinium cardiac magnetic resonance, Heart 92 2006 343-349.


