Unusual presentation of more common disease/injury

Mitral valve involvement as a predominant feature of cardiac amyloidosis

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Summary

Cardiac involvement in systemic amyloidosis carries poor prognosis with a median survival of 5 months.¹ The authors report an unusual presentation of cardiac amyloidosis in the form of predominant mitral regurgitation. The patient responded very well to medical therapy with subsequent improvement of mitral valve dysfunction. The authors would like to highlight this multisystem involvement and the presence of a complex overlap of systemic features.

BACKGROUND

Patients with renal amyloidosis often have cardiac involvement. The common cardiac manifestations include effort intolerance and arrhythmias due to myocardial infiltration. Predominant valvular involvement with minimal myocyte infiltration is rare. Data on the prognosis of patients with limited involvement is scanty. Our case report discusses a rare presentation and the excellent clinical response to medical therapy.

CASE PRESENTATION**History**

A 34-year-old Caucasian male complained of lethargy and effort-related breathlessness over a period of 8 weeks. At presentation, he described NYHA class III symptoms. He lacked any significant past medical history apart from hypertension. There was no history of rheumatic fever. He denied any other cardiorespiratory symptoms.

Physical examination

His heart rate was 109/min, regular and his blood pressure was 140/90 mm Hg. His jugular venous pressure (JVP) was not elevated. General inspection was unremarkable. He did not have any marfanoid features. There was no radio-femoral or radio-radial delays. His blood pressure was equal in both the limbs. His apical impulse was of normal character and was displaced to left sixth intercostal space at mid clavicular line. He was found to have mild pitting pedal oedema and a loud grade 3 pan systolic murmur over the apex, which radiated anteriorly with third heart sound (S3). There was no evidence of any neurological dysfunction. There was no organomegaly.

Initial investigations

His electrocardiogram (ECG) showed left ventricular hypertrophy with strain pattern (based on Sokolov-Lyon's criteria, S V1+ R V5 or V6 = 36 mV normal, more than 35 mm indicates LVH, figure 1). Chest x-ray showed cardiomegaly with increased broncho vascular markings with no peri-hilar calcific shadows. His blood tests revealed renal

failure with sodium 140, potassium 5.5, urea 13.7 (all in mmol/l) and creatinine 209 mol/l. His liver function tests were normal albeit an albumin of 23 g/dl. His calculated eGFR was 35 ml/min/1.72 m² and was suggestive of grade 3 chronic kidney disease (CKD). His urine dipstick showed 3+ protein, trace of blood and 1+ glucose. His fasting blood sugar was 5.9 mmol/l. His haemoglobin was 11.3 g/dl, white cell count was 9.3×10⁹, platelet count was 322×10⁹ and corrected calcium was 2.42 mmol/l. His serum lipid profile showed cholesterol 8.44 (2.5–5.0), triglycerides 3.31 (0.4–2.0), HDL cholesterol 0.77 (1.0–2.0) and LDL cholesterol 6.2 (1.0–3.0), all in mmol/l. His thyroid function tests showed free T4 15.6 pmol/l (9.2–24.5 pmol/l) and thyroid stimulating hormone (TSH) 1.83 mU/l (0.20–4.50 mU/l). His cardiac troponin I was 0.33 g/l (cut-off value for acute coronary syndrome is 0.40 g/l). A diagnosis of acute renal failure of unknown aetiology was made.

Renal investigations

He was found to have nephrotic range proteinuria (14.62 g/24 h, normal 0.13 g/24 h). Autoimmune serology was negative. His serum ferritin levels were 66 g/l. His immunoglobulin studies showed hypogammaglobinaemia, 2.28 g/l. Serum electrophoresis showed raised α -2 microglobulin. His mid stream urine culture was negative and his ultrasound examination of the kidneys showed left kidney size of 12.4 cm and right kidney size of 12.7 cm with four small cysts each in both kidneys with largest of them measuring 2 cm. His bone marrow examination (aspirate and trephine) showed active erythropoietic bone marrow with 4–5% of blast cells. Normal myeloid and lymphoid activity was observed.

Cardiac investigations

Subsequently, trans-thoracic echocardiography showed moderate to severe eccentric MR directed anteriorly into a dilated left atrium (4.8 cm, normal 2.7–3.8 cm). There was posterior mitral valve leaflet dysfunction in the form of diminished excursion. The rest of the mitral subvalvular apparatus appeared normal except minimal thickening in

Figure 1 ECG showing the presence of left ventricular hypertrophy with voltage criteria. This appearance is unusual in patients with cardiac amyloidosis as they often have small voltage complexes despite the presence of left ventricular hypertrophy like appearance in trans-thoracic echocardiography.

posterior papillary muscle. There was no mitral valve prolapse. He had mild concentric LVH (wall thickness 1.32 cm, upper limit of normal 1.20 cm) and moderate left ventricular dilatation (LV diameter 6.18 cm in diastole, normal 3.9–5.3 cm). LV systolic function was mild to moderately impaired and there were no regional wall motion abnormalities. There was evidence of restrictive dysfunction as mitral valve inflow velocity (E/A) ratio was 2.92, normal 1–1.5) with a deceleration time of 128 ms, (normal 150–220 ms) (videos 1–3). The mitral valve inflow Doppler showed short deceleration time with increased E (filling) velocities and no variations with normal respiration, which are the hall marks of restrictive filling pattern. The mitral valve dysfunction was secondary to reduced posterior valvular excursion without obvious thickening of leaflets but careful review of the images revealed that the mechanism of regurgitation is most probably due to the posterior papillary muscle dysfunction with minimal thickening. His right ventricle was normal in size and function. Mild tricuspid regurgitation was noted with estimated pulmonary artery pressure 35 mm Hg. There was no significant LV outflow tract gradient. A trace (<1 cm) of global pericardial effusion was observed without any evidence of cardiac tamponade. There were no visible atrial thrombi. Estimated ejection fraction by ‘eye-balling’ was approximately 45%. This level would be considered as abnormal in patients with severe mitral regurgitation as this reflects the absence of a hyperdynamic ventricle and thereby indicates impairment of systolic dysfunction. Transoesophageal echocardiography was considered but was not performed because of good quality trans-thoracic images, absence of clinical suspicion of infective endocarditis and patient’s reluctance. He was monitored with telemetry for 1 week and the recordings revealed no arrhythmias.

Video 1. Parasternal long axis view demonstrating mild left ventricular hypertrophy and diminished excursion of posterior mitral

valve leaflet. Trace pericardial effusion is evident. 10.1136/bcr.08.2008.0821v1

Video 2. Apical four chamber view showing diminished excursion of posterior valve leaflet but with minimal thickening. 10.1136/bcr.08.2008.0821v2

Video 3. Colour doppler showing severe eccentric mitral regurgitation with reduced excursion of posterior mitral leaflet. 10.1136/bcr.08.2008.0821v3

DIAGNOSIS

Rectal biopsy confirmed the diagnosis of amyloidosis (figures 2 and 3) and the subsequent serum amyloid protein (SAP) isotope scan was suggestive of the diagnosis of AL (primary) type amyloidosis but this is not specific for cardiac amyloidosis due to the ‘blood pool’ effect in the cardiac chambers. Right ventricular endomyocardial biopsy was declined.

OUTCOME AND FOLLOW-UP

His amyloidosis was treated with cyclophosphamide, dexamethasone (which was gradually up titrated to avoid volume overload and cardiac decompensation) and thalidomide. His heart failure therapy included beta blockers (bisoprolol 5 mg) and diuretics (bumetanide 2 mg, spironolactone 12.5 mg). Angiotensin converting enzyme inhibitors were avoided due to the risk of worsening renal profile and his persistent high serum levels of potassium (5.2 mmol/l).

His renal function remained stable with a creatinine of 265 mmol/dl. His NYHA status has improved to class II symptoms with medical therapy. Repeat echocardiography showed very mild mitral regurgitation and overall improvement in left ventricular dysfunction. He remains clinically stable after 1 year. His exercise tolerance improved to half a mile on the level and he is able to perform his daily activities without limitation.

Figure 2 Medium power examination of rectal mucosal tissue stained with Congo red. The areas of amyloid deposition are shown. The rest of the mucosal architecture remains unaltered.

Figure 3 High power examination of the rectal mucosal tissue showing intercellular deposition of amyloidosis.

DISCUSSION

Amyloidosis is a systemic illness with a large spectrum of clinical presentation and varied prognosis.¹ Cardiac amyloidosis occurs usually in AL type amyloidosis due to the deposition of low molecular weight proteins in the intercellular spaces of cardiac myocytes and carries worse prognosis.²

Cardiac amyloidosis is rare among Caucasians (0.6%).³ The common clinical presentation of cardiac amyloidosis results from the infiltrative cardiomyopathy secondary to diffuse amyloid deposition of the ventricles. Patients often present with features of congestive cardiac failure and predominantly right heart failure.⁴ Other cardiac manifestations include syncope and angina. Renal involvement often accompanies cardiac amyloidosis and makes both diagnosis and treatment challenging.

Cardiovascular examination may reveal elevated JVP, bipedal oedema, hypotension, third heart sound and soft systolic murmur. ECG shows low voltage complexes (in 46%) or pseudo-infarct pattern.⁴ Trans-thoracic echocardiogram forms the cornerstone in the diagnosis of cardiac amyloidosis. Echocardiographic findings include thickened ventricular and septal walls, dilated atria, small sized ventricular cavity and a 'speckled' appearance of the myocardium. Valvular involvement is rare and best quantified by echocardiogram. Under normal physiological conditions, left ventricular filling happens due to predominant passive filling (E filling) and minimal atrial contraction (A filling). In cardiac amyloidosis, E/A ratio is increased with rapid equalisation of the filling pressures resulting in a short deceleration time due to amyloid infiltration and thereby resulting in restriction of diastolic ventricular function. The mechanisms for changes in E/A ratio in restrictive filling are described elsewhere.⁵ Coronary angiography is often normal and right heart studies may show elevated right heart pressures. Cardiac MRI shows late and global subendocardial enhancement. The combination of low voltage complexes on ECG and thickened interventricular septum on echocardiography has been shown to be highly specific for diagnosis of cardiac amyloidosis.⁶ Technetium-labelled SAP radioisotope scan can identify tissue infiltration of amyloid fibrils. This test is not useful in cardiac amyloidosis due to the presence of large amount of circulating blood in cardiac chambers, which makes the differentiation of myocardial infiltration more difficult to interpret. However, although LVH seen in these cases would not be incompatible with diffuse myocardial infiltration; we believe this finding is due to the existence of hypertension. A higher prevalence of 'silent' AF and mural thrombi in this group is well known. But, the absence of a giant left atrium (more than 5.5 cm), absence of stenotic mitral valve lesion, absence of severe left ventricular dysfunction, lack of 'auto contrast' in the chambers and the absence of LV aneurysm led us to believe the risk of cardiac thrombo-embolic event to be low in this case.

Cardiac involvement isolated to the mitral valve as happened in our patient is rare and has been reported only a few times in the literature.^{7,8} Mitral valve dysfunction in cardiac amyloidosis can be due to local amyloid deposition, chordal rupture and local ischaemia or secondary to mitral annular dilatation.

The differential diagnosis of light chain cardiac amyloidosis includes various aetiologies of infiltrative

cardiomyopathy such as sarcoidosis, haemochromatosis, senile cardiomyopathy and endomyocardial fibrosis. Haemochromatosis is associated with iron overload and serum ferritin levels more than 1000 g/l. Sarcoidosis is diagnosed by classical peri-hilar shadows on chest x-ray and often associated with raised serum calcium. Endomyocardial fibrosis is a hyper-eosinophilic syndrome with good response to steroids.

We propose that the mitral valve dysfunction seen in our patient is secondary to amyloid deposits in the subvalvular apparatus, which has altered the actual physical properties of the valve resulting in incompetence. Moreover, his mitral regurgitation and symptoms of congestive heart failure improved with chemotherapy and heart failure therapy. The literature on the reversibility of mitral valve dysfunction in cardiac amyloidosis is scanty. Combination chemotherapy of patients with cardiac amyloidosis has been shown to produce remission in up to 21%.⁹ The prognosis of the illness in this subset of patients with isolated valvular involvement is unknown but the reversibility of mitral regurgitation as happened in our case may suggest a better prognosis. In addition, as in our case, the presence of large voltage complexes in the ECG of patients with suspected cardiac amyloidosis does not refute the diagnosis.

LIMITATIONS

The extent of any coronary artery disease is unknown in our patient as he declined cardiac catheter studies. However, there were no surrogate pointers to suggest significant coronary atheroma, with no significant cardiac enzyme rise, and no regional wall motion abnormalities seen on echo. His gross dyslipidaemia was secondary to his nephritic syndrome. A mild rise in cardiac troponin is often associated with cardio-renal failure and may not signify significant coronary artery disease. However, the possibility of regional ischaemia driven mitral valve dysfunction cannot be excluded.

Our patient's clinical improvement is likely to be due to both the combination of his chemotherapy for amyloidosis and his heart failure therapy. The exact contribution of each in our case is virtually impossible to substantiate without a further pool of case report analyses. However, the rarity of the condition makes this a daunting challenge.

Complete remission of cardiac symptoms has been reported in small-scale chemotherapy trials.⁹ However, near complete resolution of mitral valve dysfunction is unusual and unreported. Endomyocardial biopsies would have helped to confirm and monitor the disease process but were not carried out.

CONCLUSION

This case report highlights the need to evaluate multi-system involvement in patients with renal amyloidosis. We would like clinicians to be aware of this unusual manifestation of cardiac involvement of amyloidosis and the reversibility of mitral valve dysfunction with medical treatment. The outlook of patients' who are symptomatic with cardiac amyloidosis is poor. However, early and timely therapy for this multi-system disease will improve the symptoms and may improve prognosis.

Learning points

- ▶ Patients presenting with renal amyloidosis should be assessed for cardiac involvement.
- ▶ Cardiac involvement in amyloidosis can present as mitral valve dysfunction.
- ▶ Intensive medical therapy may reverse cardiac involvement.

Competing interests None.

Patient consent Obtained.

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