CASE REPORT

Senile cardiac amyloidosis: an underappreciated cause of heart failure

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SUMMARY

This case presents a patient with biopsy-proven, wild-type transthyretin (TTR) senile amyloidosis. The case was that of a man in his early 70s who presented with gradually progressive symptoms and signs of heart failure. The recent history included an episode of severe pancreatitis secondary to cholelithiasis and subsequently (and incidentally) noted hepatomegaly and marked ascites. Further evaluation of the aetiology of the heart failure, through echocardiography, coronary angiography and endomyocardial biopsy, led to an exact diagnosis of SSA. The patient is being treated with conventional heart failure medications while consideration is given to the use of diflusal as an antiamyloidogenic small molecular stabiliser of TTR. Monitoring and further management advice are being coordinated by the National Amyloidosis Centre.

BACKGROUND

Three main subtypes of cardiac amyloid are recognised, namely light chain (AL), hereditary (usually but not exclusively due to a mutation of transthyretin (TTR)) and senile (wild-type TTR) amyloid. Senile amyloidosis (SSA) is a clinical condition which may result in extensive deposition of TTR-derived fibrils within the myocardium. This can ultimately lead to heart failure, rhythm disturbance, embolic events and, ultimately, death. To date, the majority of diagnoses and descriptions of disease progression have been largely based on postmortem studies. This is because the condition remains underrecognised and because, until recently, no treatment options existed to address the underlying disease process of amyloid deposition in SSA.

With new advances in management options and ongoing clinical trials, it is important to update and increase physicians' awareness of SSA.

CASE PRESENTATION

A 72-year-old Caucasian man, with no relevant family history, presented to an emergency department with abdominal pain. He was diagnosed with pancreatitis secondary to cholelithiasis. Three years later, he re-presented with further abdominal discomfort, when note was made of hepatomegaly. Radiological and ultrasound imaging demonstrated a large pancreatic pseudocyst, hepatic congestion and marked ascites. Management initially consisted of the insertion of recurrent peritoneal drains. Over the following 9 months, he developed progressive breathlessness and peripheral oedema. There was no chest discomfort or palpitations and no evidence of neuropathy, macroglossia or skin petechiae.

Examination revealed normal heart sounds with no third heart sound and the chest was clear to auscultation.

INVESTIGATIONS

An initial ECG showed sinus rhythm, first-degree atrioventricular block and left axis deviation but a notably not low voltage. An ECG showed features consistent with amyloid heart disease with increased left ventricular (LV) wall thickness (1.4 cm), mildly impaired systolic function (ejection fraction 45–50%) and a reduced long-axis function on tissue Doppler analysis (S-wave at the lateral wall of 70 cm/s). Both atria were dilated (left atrium 3.9×6.7 cm, right atrium 4.0×6.2 cm in an apical four-chamber view). The right ventricle was not dilated but exhibited mild concentric 'hypertrophy' and reasonable right ventricular (RV) free wall motion (TAPSE=1.9 cm). There was grade III diastolic dysfunction, as supported by a mitral E/A ratio of 3.3, a deceleration time of 154 ms (severe when <150 ms) and an E/E' of 14 (normal <8). There was also a thickening of the aortic valve but no significant valvular dysfunction and a small pericardial effusion. The remaining valves showed normal morphology with moderate tricuspid regurgitation and an estimated pulmonary artery pressure of 42+ JVP mm Hg. The inferior vena cava measured 2.5 cm in diameter with no notable change on sniffing. Coronary angiography was performed and demonstrated left anterior descending atherosclerotic disease which was stented. The right and circumflex coronary arteries were unremarkable. A cardiac MRI scan confirmed a generalised thickening of the LV myocardium (up to 17 mm in the septum) with ventricular function (LV ejection fraction 60% and RV 43%) and volumes within normal limits. Both the atria were slightly dilated. Delayed postcontrast (Gadovist) showed typical circumferential enhancement of the LV myocardium, a feature highly suggestive of amyloid heart disease. A cardiac biopsy confirmed amyloid of TTR type. A technetium diphosphono-propanodicarboxylic acid (Tc-DPD) scintigraphic scan was positive for myocardial uptake (grade II), a feature highly suggestive of TTR-related amyloidosis.¹ Direct sequencing of the TTR gene did not detect any mutation.

Other investigation included a normal full blood count, renal electrolytes and liver enzymes, serum electrophoresis and Bence-Jones protein. The international normalised ratio (INR) was elevated (1.4), as were the brain natriuretic peptide (267 pmol/l), ascitic albumin level (411 mg/l) and urinary protein : creatine ratio (49 mg/mmol).

To cite: Shah S, Dunga J, Dubrey SW. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007635

DIFFERENTIAL DIAGNOSIS

The possibility of a hereditary form of TTR-derived amyloidosis was excluded by genetic analysis. In addition, there was no family history (not obligate), and organ involvement appeared to be confined to the heart.

TREATMENT

Treatment was started with aspirin and clopidogrel after coronary stenting, in addition to the long-standing medication for diabetes and thyroxine replacement therapy. Further management consisted of fluid restriction and conventional heart failure therapies (ACE inhibitors and diuretics). Consideration is being given to the use of diflusinal. Current hesitation is due to the potential adverse effects of giving diflusinal to a patient already committed (recent coronary stenting) to a course of aspirin and clopidogrel.

The nonsteroidal anti-inflammatory drug diflusinal and a newer development tafamidis have been shown to stabilise the soluble TTR tetrameric structure in vitro and in vivo,² the effect being to prevent a conformational change in the TTR with a resultant loss in 'solubility' and precipitation to form an amyloidogenic nidus. Both compounds are currently undergoing further clinical investigation.

OUTCOME AND FOLLOW-UP

Symptoms of breathlessness have improved, as has the peripheral oedema, but the patient continues to have moderate ascites, the latter possibly confounded by the presence of his pancreatic pseudocyst. Regular surveillance by the National Amyloid Centre is also in place. SSA usually follows a gradually progressive course, in contrast to other recognised forms of cardiac amyloidosis and notably AL amyloid. SSA has always offered a better prognosis than AL amyloid (very likely contributed to by the inherent toxicity of circulating light chains), and with the development of new therapies, the prognosis for SSA should hopefully improve further.

Echocardiographic follow-up is in place to follow any likely progression of cardiac involvement. It is hoped that the patient will be eligible to enter a clinical trial of therapy for TTR cardiac amyloid disease.

DISCUSSION

The true prevalence of SSA is unknown in living patients. Over decades, it has been accepted that the finding of amyloid (TTR wild type) in the myocardium of elderly men is common at postmortem studies.³ However, it is unproven whether the prevalence of amyloid deposition in the autopsy population is proportional to the prevalence of SSA in the living population.⁴ SSA presents, almost universally, with cardiac involvement. On occasions, this may be massive and surpass features seen in AL amyloidosis.⁵ There are, however, some case reports showing association with carpal tunnel syndrome.⁶ Recent studies highlight that senile cardiac amyloidosis is an underrecognised

entity, usually being recognised on microscopy of the myocardium, following autopsy.^{7,8} It has been hypothesised that the condition remains under-recognised owing to the following reasons:

- ▶ A reduced attention to elderly patients in general;
- ▶ Underuse of cardiac testing to investigate the aetiology of heart failure;
- ▶ Misinterpretation of echocardiographic findings;
- ▶ A minimalistic approach to investigating elderly patients even when a diagnosis of amyloid is considered and
- ▶ An anxiety to performing endomyocardial biopsies (by both patient and physician).

A recent review argues that senile systemic amyloidosis is significantly under-represented and may be as common as, or more so than, AL amyloid.⁵

Learning points

- ▶ Senile amyloidosis (SSA) is an underrecognised cause of heart failure in the elderly.
- ▶ It is significantly more common in men.
- ▶ SSA should be considered in elderly men (usually over 70 years of age) with thick walled hearts and on echo and clinical features of heart failure.
- ▶ A tissue biopsy is a requisite to obtain a definitive diagnosis.
- ▶ TC-DPD scintigraphic scanning is a recent addition to the diagnosis of transthyretin-related amyloid heart disease.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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