Coexistent asymptomatic myeloma and hereditary cardiac amyloidosis: an unusual case of heart failure

Introduction

A 76-year-old Afro-Caribbean man presenting with heart failure was diagnosed with isolated cardiac amyloid. He had evidence of myeloma on bone marrow biopsy suggesting AL amyloid, the commonest type of systemic amyloidosis, as the underlying cause. He had no other myeloma-related organ damage. However, endocardial biopsy revealed amyloid fibrils composed of transthyretin and genetic typing established heterozygozity for the valine to isoleucine mutation at position 122 (Val122Ile). The diagnosis was therefore hereditary systemic amyloidosis as a result of a genetic transthyretin variant (ATTR) causing cardiac amyloidosis and coexistent asymptomatic myeloma. This requires symptomatic treatment of heart failure only.

This article discusses a rare cause of heart failure and uses this case to illustrate that histological confirmation of the amyloid-causing protein is essential. Mistaken assumption of AL amyloid could have resulted in inappropriate cytotoxic therapy targeting the plasma cell clone.

Discussion

Amyloidosis arises from the abnormal accumulation of misfolded, insoluble protein that aggregates in beta-pleated sheets. To date over 20 proteins are known to form amyloid fibrils (Sipe et al, 2010). As a result of excess production or a genetic mutation, proteins form beta-pleated sheets (rather than the normal alpha helix) which align in an antiparallel manner forming proteolysis-resistant fibrils. This commonly affects the heart, kidney and nervous system but can affect any tissue except the brain.

Systemic amyloidosis is classified according to its causative protein and can vary by clinical features and fibril distribution but is ultimately differentiated by immunohistochemistry of affected tissues (or more recently laser capture microdissection and mass spectrometry). AL amyloid is the most common and is caused by immunoglobulin light chain fragments produced by clonal plasma cells. Secondary systemic (AA) amyloid occurs in chronic inflammation and is caused by proteolytic fragments of serum amyloid A protein.

A small proportion of individuals who inherit one of a number of mutated proteins develop hereditary systemic amyloidosis. ATTR is the most common form of hereditary amyloidosis and is caused by dominant mutations in the transthyretin gene. Four per cent of Afro-Caribbeans possess the aberrant DNA sequence Val122Ile, which has a low but uncertain penetrance, and typically presents in elderly patients with isolated cardiac amyloidosis (Jacobson et al, 1997; Jiang et al, 2001). Senile systemic amyloidosis presents similarly and is a slowly progressive condition caused by fibrils derived from wild type transthyretin affecting patients over 70 years of age.

In cardiac amyloidosis, findings are commonly present on electrocardiography and echocardiography. On electrocardiography, low amplitude QRS complexes (≤1 mV in precordial leads or ≤0.5 mV in all limb leads), a pseudoinfarction pattern (Q waves in consecutive leads), conduction delays as well as arrhythmias (most commonly atrial fibrillation) are seen. On

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Case Report

A 76-year-old Afro-Caribbean man presented with progressive exertional dyspnoea and gross peripheral oedema up to the chest wall. He had a background of diabetes, hypertension and hypercholesterolaemia with no significant family history.

On examination, he had signs of congestive cardiac failure. He did not have a postural drop, macroglossia, hepatosplenomegaly or any significant neurology. His electrocardiogram revealed atrial flutter with variable block and low amplitude QRS complexes of <1 mV in the precordial leads. An echocardiogram showed normal left ventricular size, severe concentric left ventricular hypertrophy with a wall thickness of 2 cm and severe systolic impairment (ejection fraction 30%). There was increased myocardial echogenicity suggestive of possible cardiac amyloidosis. He had a normal full blood count, renal function and calcium level. Troponin T was within normal range at 0.1 ng/ml but brain natriuretic peptide (NT-pro BNP) was raised at 430 pmol/litre.

Serum and urine electrophoresis detected a faint lambda light chain band and serum free light chain assessment demonstrated a lambda excess: kappa light chain 9.5 mg/litre, lambda light chain 1080 mg/litre, ratio 0.01 (normal ranges 3.3–19.4 mg/litre, 5.71–26.3 mg/litre, 0.26–1.65 respectively). There were no lytic lesions on skeletal survey. A bone marrow trephine biopsy was diagnostic of myeloma with lambda restricted plasma cells comprising 75–80% of total marrow cells. I^{123} labelled serum amyloid P component scintigraphy, which does not visualize the heart, showed no visceral uptake suggesting isolated cardiac amyloid deposition. An endocardial biopsy confirmed typical Congo Red positive deposits (*Figures 1a* and *b*). Immunohistochemistry confirmed amyloid to be of transthyretin type (*Figure 1c*). Sequencing of the transthyretin gene established heterozygozity for the valine to isoleucine mutation at position 122. The diagnosis was hereditary systemic amyloidosis as a result of a genetic transthyretin variant causing cardiac amyloidosis and coexistent asymptomatic myeloma.

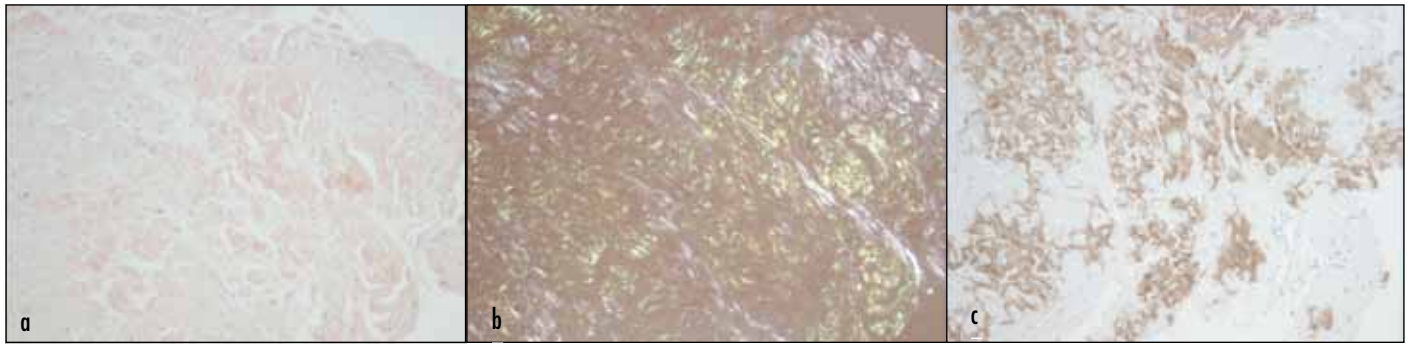

Figure 1. a. Endocardial biopsy stained with Congo Red and (b) showing apple-green birefringence in polarized light indicative of amyloidosis. c. Positive immunohistochemical staining for transthyretin.

echocardiography, the most common changes are granular sparkling and left ventricular wall thickening in the absence of hypertension (Desai et al, 2010).

Treatment of cardiac amyloid varies according to the type of amyloid and consists of eliminating the disease-causing protein where possible, supportive therapy or in select cases transplant of affected organs. However, identifying the amyloid-type may not be straightforward as there can be more than one potential amyloid causing protein. Without tissue, misdiagnosis of hereditary as AL amyloid occurs in 9.7% of cases (Lachmann et al, 2002; Comenzo, 2009). Relevant to this patient, plasma cell clones and the transthyretin Val122Ile variant are both common in elderly Afro-Caribbean men (Kyle et al, 2006).

Conclusions

Although heart failure is a common diagnosis, and amyloidosis an unusual cause, it should be considered in patients with abnormalities noted on electrocardiography and echocardiography, especially in patients with a monoclonal protein or from certain ethnic groups. In elderly Afro-Caribbean patients with isolated cardiac amyloid, a distinction has to be made between AL, hereditary ATTR and SS amyloidosis – which is only possible with biopsy of affected tissue. In this case, Val122Ile was identified by polymerase chain reaction of genomic DNA and on the basis of his bone marrow biopsy findings, this patient also has myeloma with no evidence of myeloma-related end-organ damage. A presumption of cardiac AL amyloidosis would have resulted in commencing cytotoxic therapy with significant potential for morbidity and possible treatment related mortality. However, the concurrent diagnosis of hereditary ATTR and asymptomatic myeloma warrants medical management of his cardiac amyloid and close monitoring, but no therapy targeting the plasma cell clone at this stage. BJHM

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KEY POINTS

- Cardiac amyloid is a rare cause of a common condition.
- Biopsy of affected tissue allows confirmation of amyloid deposition and fibril typing.
- In an individual, there may be more than one potential cause of amyloidosis so biopsy is essential.
- Mistaken assumption of AL amyloidosis can result in inappropriate cytotoxic therapy.