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lesson of the month (1)

Diagnostic dilemma and sudden death outcome: a case of amyloid cardiomyopathy

Despite many advances in treatment, amyloid heart disease still portends a poor outcome. Around 50% of patients will suffer a sudden arrhythmic death. As in the case described, this may happen before the patient has received sufficient treatment to curtail the amyloidogenic process.

Lesson

A 50-year-old Asian woman presented with shortness of breath, intermittent dizziness and general malaise of 2 months' duration. Examination revealed low blood pressure (108/60 mmHg) and a nodal bradycardia of 38 beats per minute. Teeth indentation in the lateral border of the tongue raised the possibility of macroglossia. The patient was on no medication and had no family history of note. An electrocardiogram showed low voltage in all limb leads (mean 0.3 mV), with Q waves in leads V1–V3. On echocardiography, she had mild left ventricular hypertrophy (mean 13 mm), with restrictive features on Doppler echocardiography and a mildly reduced ejection fraction of 45%. All blood test results were normal aside from a high level of troponin I of 0.47 ng/ml (normal <0.04 ng/ml). A cardiac magnetic resonance imaging (MRI) scan showed transmural gadolinium enhancement, with a significant region in the basal inferolateral wall, unremarkable biventricular function, and small pericardial and pleural effusions. The differential diagnosis was felt to include cardiac ischaemia, vasculitis and possibly sarcoidosis; findings were not typical for amyloidosis. A coronary angiogram revealed normal coronary arteries. A dual-chamber pacemaker was implanted, and the patient's symptoms improved.

Six months later the patient presented with significant peripheral oedema that extended to the abdomen and sacrum, hypotension (95/68 mmHg) and worsening dyspnoea. A repeat troponin test found high levels of 0.23 ng/ml, and levels of N-terminal proBNP (NT-proBNP) were markedly increased at 1,078 pmol/l. On echocardiography, the walls had further thickened to 14 mm and the ejection fraction had further reduced to 35%. Repeat MRI could not be performed due to the implanted pacing system, but an endomyocardial biopsy revealed amyloid deposits in the myocardial interstitium and the walls of the small arterioles, which stained with an anti-kappa antibody. Radiolabelled serum amyloid P (SAP) component scintigraphy showed amyloid within the spleen but not elsewhere (cardiac amyloid deposits are not visualised by this procedure) (Fig 1). A bone marrow trephine showed a plasma-cell infiltrate of 15% (aspirate 17%), with kappa light-chain restriction. A skeletal survey for osteolytic lesions was negative. No paraprotein was detected, but levels of free light chains of kappa isotype in the serum were markedly elevated at 562 mg/l (normal 3.3–19.4 mg/l) (Fig 2), which confirmed a kappa-secreting plasma-cell dyscrasia. The diagnosis was therefore systemic amyloid light-chain (AL) amyloidosis complicating a kappa light chain-secreting plasma-cell dyscrasia. The patient was started on monthly cycles of cyclophosphamide, thalidomide and dexamethasone (CTD) and achieved an excellent haematological response. One week after completing her fourth cycle of CTD, she developed ventricular fibrillation while shopping. Despite full resuscitative efforts, she developed pulseless electrical activity and died.

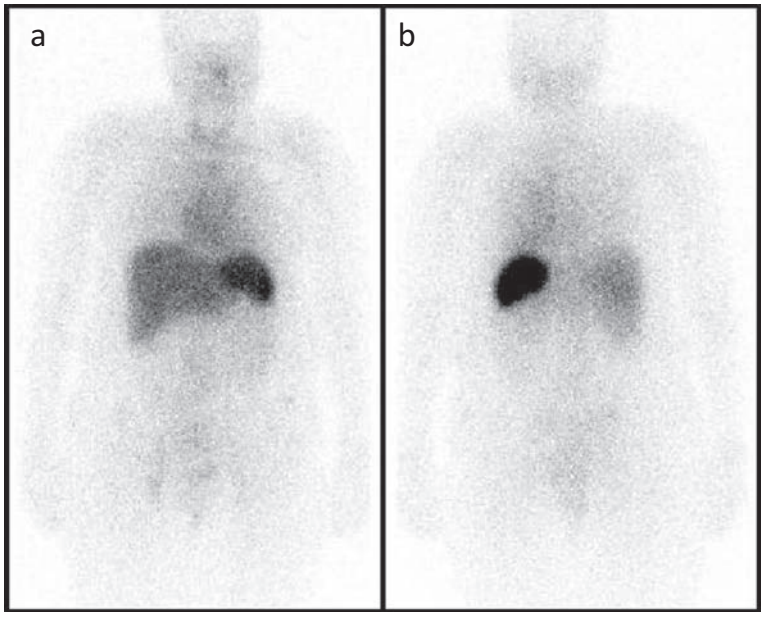

Fig 1. Whole-body, 123-iodine-labelled serum amyloid P component (SAP) scintigraphy showing uptake in spleen on anterior (a) and posterior (b) views.

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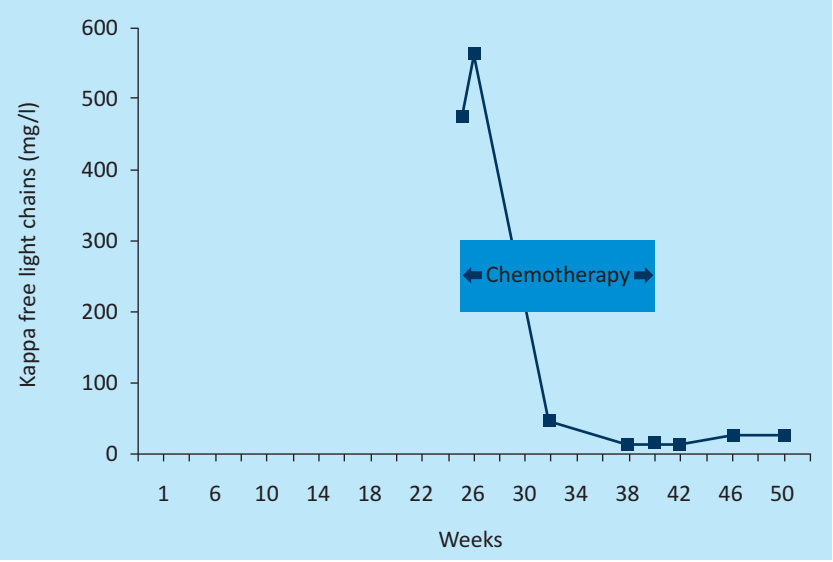

Fig 2. Reduction in kappa-immunoglobulin free light chains in response to four cycles of cyclophosphamide, thalidomide and dexamethasone (CTD) chemotherapy.

Discussion

This case illustrates the difficulty of diagnosing amyloid and the all-too-frequent delays in establishing the diagnosis, even in cases such as this, where there was clinical suspicion. In our patient, both the presenting symptoms, including a suspicion of macroglossia, and initial electrocardiogram suggested amyloidosis. A bradycardia with requirement for pacing, Asian race and the appearances on the cardiac MRI scan indicated sarcoidosis. The positive troponin, although also a feature of cardiac amyloid, suggested possible ischaemic aetiology. A definitive diagnosis was eventually established following Congo red and immunohistochemical staining of the cardiac biopsy, a bone marrow examination and, with the assistance of the National Amyloidosis Centre, demonstration of amyloid in the spleen by SAP scintigraphy and high levels of free immunoglobulin light chains in the serum. Early diagnosis of amyloid and amyloid-fibril typing is critical, but, unfortunately, no diagnostic test short of a tissue biopsy is reliable. Indeed, reduced QRS voltages on electrocardiography may be absent in up to 50% of patients with cardiac amyloidosis, and diffuse late gadolinium enhancement on cardiac MRI scans, although characteristic of cardiac amyloidosis, may not be seen; amyloid thus ought to be considered in any patient with abnormal gadolinium kinetics. Diagnostic delay, particularly in cardiac amyloidosis, may prevent the patient from receiving the most effective therapy and is associated with a worsening prognosis.

Cardiac involvement portends the worst prognosis in AL amyloidosis, although regression has been described, even from the heart, after achievement of an effective haematological response.[1,2] Our patient made clear haematological and clinical progress after starting chemotherapy. A repeat SAP scan indicated possible early regression of the splenic amyloid deposition. She was requiring less diuretic, and we anticipated a gradual but definite further improvement in her symptoms of heart failure. No electrocardiograms had indicated any propensity to tachyarrhythmia, but our patient still succumbed to ventricular fibrillation.

The sinister association this disease has with sudden death, despite a clear response to therapy, remains an important issue.[3] Studies have not shown any survival benefit from implantable defibrillators,[4,5] and no studies have yet examined the benefit of biventricular pacing.

References

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