Systemic lambda light-chain deposition presenting with predominant cardiac involvement

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Summary: An 82 year old woman with suspected Bence Jones myeloma developed intractable fluid retention presumed secondary to cardiac failure. In addition she experienced angina pectoris, and required permanent cardiac pacing for symptomatic sinus bradycardia. Postmortem studies revealed prominent myocardial and renal deposits of lambda light-chains which were Congo Red negative, and had a non-fibrillar ultrastructure. Non-amyloidotic light-chain deposition is uncommon, and a rare cause of cardiac disease. Previous work regarding possible pathogenetic mechanisms, clinical and laboratory features and treatment is reviewed.

Introduction

Systemic deposition of free immunoglobulin light-chains can cause local tissue injury. Deposits may be amyloidotic or non-amyloidotic, and both forms may cause similar organ dysfunction. We describe a patient with cardiac symptoms due to non-amyloidotic deposition of lambda light-chains in the myocardium.

Case report

A 82 year old Caucasian woman was admitted to hospital with a 10 day history of breathlessness, ankle swelling and intermittent dizziness. She had suffered angina pectoris for 5 years, and latterly developed signs of cardiac failure responsive to diuretics. On examination she had a pulse of 54/minute and blood pressure of 155/65 mmHg. The jugular venous pressure was not elevated, but there was bilateral pitting oedema. Auscultation revealed soft ejection systolic and early diastolic murmurs.

Chest radiography was normal and electrocardiography showed a sinus bradycardia with poor r wave progression. Serum urea and electrolytes and full blood count were normal, and the erythrocyte sedimentation rate was 17 mm/hour. The serum albumin was only mildly depressed at 36 g/l (normal range 37–49 g/l) despite marked proteinuria (5,340 mg/l). Monoclonal lambda light-chains were detected in the urine but not the serum. Forty-eight hour Holter monitoring showed persistent sinus bradycardia with intermittent left bundle branch block. Echocardiography revealed trivial aortic regurgitation only. Increased diuretic therapy reduced the peripheral oedema, and her dizziness and breathlessness were relieved by a temporary, and then permanent, pacemaker.

Increasing breathlessness necessitated readmission 2 months later. There was marked peripheral oedema and her jugular venous pressure was elevated. Urinalysis again showed heavy proteinuria. Serum biochemistry was unremarkable although immunoglobulin levels were low; an underlying Bence Jones myeloma was suspected, and the possibility of cardiac amyloidosis considered. Repeat electrocardiography, echocardiography and chest radiography were unchanged. Congo Red staining of a rectal biopsy was negative. A MUGA (multigated acquisition) scan was normal (left ventricular ejection fraction 60%) and a technetium pyrophosphate myocardial scan unremarkable. Left and right heart catheterization were performed. Trivial aortic regurgitation and minimal coronary disease were identified. Left ventricular contraction was mildly dyskinetic secondary to pacing but otherwise normal. Ventricular filling pressures were normal although the left ventricular pressure trace suggested a 'dip and plateau' pattern. Pulmonary artery and capillary wedge pressures were also normal. The patient’s condition
chains, are described were Congophobic (although well-preserved tissue architecture (haematoxylin microscopy embalming, chain deposits usually concentrated in the glomeruli with faint peritubular staining (Figure 2). Glomerulosclerosis and all sections consist of fibrillar substructure renal biopsy showed features of moderate nodular tissue architecture throughout. The renal biopsy showed features of moderate nodular glomerulosclerosis and all sections were Congo Red negative. However, when stained with thioflavine-T, prominent amorphous extracellular deposits were seen in the myocardium, kidneys and spleen. The myocardial deposits were found in an interstitial and perivascular distribution (Figure 1), whilst the renal deposits were concentrated in the glomeruli with faint peritubular staining (Figure 2). Paraffin-embedded sections of myocardium and kidney were prepared for electron microscopy. Electron-dense deposits with a mixed granular and fibrillar substructure (Figure 3) were seen in a similar distribution. Indirect immunoperoxidase staining for kappa and lambda light-chains was negative. The rectal biopsy was re-examined and stained positively with anti-lambda (but not anti-kappa) antiserum. Finally, radiographs were reviewed post-mortem, and showed generalized osteopenia but no lytic bone deposits.

Discussion

The detection of free monoclonal immunoglobulin light-chains in urine or serum implies disorganized antibody synthesis amongst cells of B-lymphocyte lineage. An underlying plasma cell dyscrasia or lymphoproliferative disease is often responsible but in a significant minority no malignancy is detectable. In this case a Bence Jones myeloma was likely but not formally demonstrated by marrow examination pre- or postmortem.

Light-chains are poorly soluble proteins and may cause tissue injury by a variety of mechanisms. Obstructive nephropathy due to precipitation of light-chains within distal tubules is well recognized in Bence Jones myeloma, and they may also be directly toxic to proximal tubular epithelium. Light-chains may also form extracellular deposits which may be either amyloidotic or non-amyloidotic in appearance. Amyloidotic light-chain deposits usually contain lambda-class light-chains, are Congophilic, and have a fibrillar appearance on electron microscopy. Non-amyloidotic light-chain deposits were first reported in renal tissue in 1973, and similar systemic deposits were described in 1976. These latter deposits typically consist of kappa-class light-chains, are Congophilic (although often thioflavine-T positive), and usually have a finely granular ultrastructure, although occasional fibrillar areas may be seen. This deposition pattern has also been termed 'light-chain deposition disease' but this is perhaps not ideal as extracellular light-chain deposition represents a pathogenetic mechanism rather than a discrete disease entity.

It is unclear why some monoclonal light-chains form non-amyloidotic deposits while others form classical amyloidotic precipitates. Biosynthetic studies in several patients with non-amyloidotic deposits have suggested abnormalities of light-chain length and glycosylation. Furthermore non-amyloidotic light-chain deposits lack the amyloid-P component which may be essential for amyloidogenesis. Occasionally both forms of deposit occur in the same patient.

The clinical manifestations of non-amyloidotic light-chain deposition appear to be similar to those of light-chain amyloidosis. Most patients present with renal failure and non-selective proteinuria. The liver and heart may also be involved and,
although heart failure is not uncommon, it has never previously been reported to our knowledge with lambda light-chain deposition. Detailed investigations in several subjects with non-amyloidotic light-chain deposition suggest features similar to cardiac amyloidosis. In the latter the primary defect is diastolic failure with variable systolic impairment, and ventricular filling pressures are usually elevated, particularly on the left. Rapid early diastolic filling with abrupt cessation of filling in mid-diastole is reflected in the characteristic ‘dip and plateau’ left ventricular pressure waveform. In our patient cardiac catheterization was unremarkable apart from an abnormal left ventricular pressure tracing, although the filling pressures may have been normalized by prior diuretic therapy. Although she also had heavy proteinuria her serum albumin was initially well preserved and at this time her fluid retention was felt to be due to a restrictive cardiac defect. However, in the terminal phase of her illness it seems that myocardial function was otherwise well preserved and that renal involvement was the cause of her death.

Other cardiac complications of non-amyloidotic light-chain deposition include arrhythmias and myocardial infarction. Sinus bradycardia and angina pectoris have been reported rarely and in both patients kappa light-chain deposits were identified. Inter cellular light-chain deposits probably reduce myocardial compliance and impair tissue oxygenation, while deposits in intramyocardial arterioles may restrict tissue perfusion.

A combination of hypogammaglobulinaemia with either nephropathy, neuropathy or cardiomyopathy should suggest light-chain deposition. Non-amyloidotic deposits probably occur as often as light-chain amyloidosis but are diagnosed less frequently. Accurate diagnosis rests upon immunohistological and/or ultrastructural examination of biopsies from involved organs. Immunohistochemistry is not always positive and failure of immunological staining may become more prevalent with ageing of the deposits which may explain the present findings. However, the embalming process may have reduced the accessibility of antigenic binding sites on the deposited light-chains compared to those in the rectal biopsy.

As in light-chain amyloidosis, the management of non-amyloidotic light-chain deposition is unsatisfactory. There is some evidence that appropriate cytotoxic therapy may benefit those patients who have an underlying myeloma, and even those...
who do not. However, caution may be justified in the presence of cardiac involvement. Cardiotoxic agents such as doxorubicin may carry an increased risk in patients with pre-existing cardiac disease, and a case of fatal heart failure was reported recently in a subject with cardiac amyloidosis after a single dose of this drug.

Treatment of specific cardiac symptoms is also contentious. Diuretics should be used cautiously in heart failure as excessive reductions in filling pressures could reduce cardiac output and cause hypotension. The treatment of bradyarrhythmias is also problematic. Poor ventricular compliance makes atrial transport relatively more important and, without an atrial pacemaker, cardiac output may actually fall.

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