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Case Report

Diagnosis and monitoring a case of light-chain deposition disease in the kidney using a new, sensitive immunoassay

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Abstract

A 59-year-old male was diagnosed with nephrotic syndrome secondary to light-chain deposition disease. There was no other evidence of a B cell clonal disorder or amyloidosis; circulating free light chains were identified using a new immunoassay (Freelite) and used to monitor disease progression. Improvement in renal function and proteinuria following VAMP chemotherapy correlated with a reduction in circulating light-chain levels. This case demonstrates a new tool in monitoring light-chain deposition disease in the kidney.

Keywords: chemotherapy; Freelite assay; light-chain deposition disease; nephrotic syndrome

Case

A 59-year-old Caucasian male presented to nephrologists with flu-like symptoms, hypertension and swelling of the face, hands and legs. He had nephrotic range proteinuria (13.9 g protein/24 h) and serum biochemistry showed creatinine 200 μmol/l [calculated glomerular filtration rate (GFR): 73 ml/min], albumin 30 g/l and cholesterol 9.9 mmol/l. A renal biopsy showed nodular glomerulosclerosis with evidence of light-chain deposition disease (LCDD) on electron microscopy (Figure 1). Congo red staining was negative. Serum electrophoresis, immunoglobulin levels and urinary Bence–Jones protein assays were all normal.

He was referred to the Haematology Department to rule out an underlying B cell clonal disorder. Bone marrow aspirate and trephine revealed normal cellular marrow with no morphological or immunophenotypic evidence of multiple myeloma; Congo red staining was negative. A serum amyloid protein scan did not show any evidence of amyloid deposition. Serum was tested at the National Amyloid Centre using the Freelite assay, which revealed the following light-chain findings: kappa levels 526.0 mg/l (normal range: 3.3–19.4 mg/l), lambda levels 64.6 mg/l (normal range: 12.7–26.3 mg/l) and a kappa:lambda ratio of 8.14 (normal range: 0.26–1.65).

Subsequent to this he developed atrial fibrillation. A 24 h tape showed irregularities in the atrial chamber and intermittent disruption of AV node conduction. He had a dual chamber pacemaker fitted and cardiac biopsy was performed, which showed no evidence of amyloid or light-chain deposition.

His hypertension was aggressively treated (including the use of an angiotensin-converting enzyme inhibitor) and his cholesterol was controlled with a statin. Despite this, over the following 12 months his renal function deteriorated and his creatinine reached 300 μmol/l (calculated GFR: 45 ml/min). He continued to have heavy proteinuria. The risks and benefits were discussed with him and, in order to prevent progression of renal disease, he was treated with three cycles of VAMP chemotherapy (vincristine 0.4 mg/day for 4 days, doxorubicin 9 mg/m^2/day for 4 days and methylprednisolone 1 g/m^2 for 5 days per cycle). Subsequent to the chemotherapy, circulating light-chain levels decreased (Figure 2) and the kappa:lambda ratio fell to within normal range. This was accompanied by a rapid improvement in his renal function to a creatinine of ~200 μmol/l (calculated GFR: 70 ml/min). His urinary protein excretion fell to 4.4 g/24 h at 9 months after the chemotherapy. His serum albumin returned to the normal range.

He remained clinically stable for 1 year at which time the kappa:lambda ratio again began to increase. This was accompanied by a rise in serum creatinine. A further three cycles of VAMP were given and similar improvements in both renal function and light-chain levels were observed. His renal function has remained stable over 36 months after the chemotherapy (most recent serum creatinine: 184 μmol/l; calculated GFR: 75.7 ml/min; urinary protein: 0.98 g/24 h).

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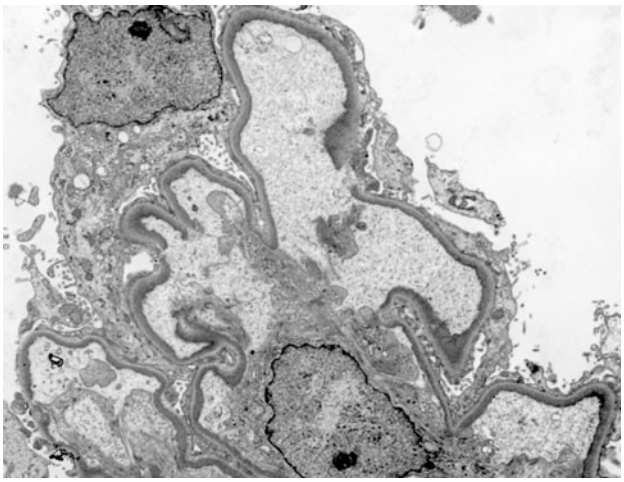

Fig. 1. Electron microscopy of the renal biopsy showing granular, electron-dense material in the tubular basement membranes.

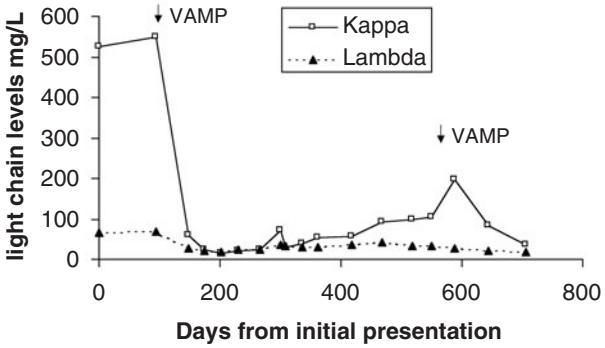

Fig. 2. Response of kappa and lambda light-chain concentrations to VAMP chemotherapy.

Discussion

LCDD is characterized by the accumulation of monoclonal light chains in various organs, including the kidneys, heart, skin, liver, spleen and nervous system. Approximately two-thirds of patients with LCDD have an underlying lymphoplasmacytic proliferative disorder, such as multiple myeloma or Waldenström's macroglobulinaemia. This is often related to systemic AL (primary) amyloidosis, as AL fibrils are derived from circulating light chains. The remainder of diseases linked with LCDD, for example essential monoclonal gammopathies, do not have evidence for a neoplastic disorder [1].

LCDD involving the kidney produces characteristic histological changes. Light microscopy shows nodular glomerulosclerosis and thickening of the tubular basement membranes. Electron microscopy reveals finely granular electron-dense material present in bands in the glomerular capillary basement membranes and along the outer aspects of the tubular basement membranes. Immunofluorescence demonstrates the fixation of monoclonal light-chain antisera all along tubular basement membranes.

Patients most often present with renal insufficiency or the nephrotic syndrome and, occasionally, early symptoms and signs may be related to liver or heart involvement. Without treatment renal function deteriorates rapidly. Several trials have shown the benefit of cytotoxic chemotherapy in suppressing the underlying clonal plasma cell dyscrasias and, therefore, the production of light chains. This has been demonstrated in light chains in AL amyloidosis where treatment options include melphalan and prednisolone [2], peripheral blood stem-cell transplantation [3] and intermediate-dose infusional regimens, such as VAD and VAMP [4].

Recently, a sensitive nephelometric immunoassay has been developed which can detect circulating light chains in the absence of a detectable whole paraprotein and can quantify serum concentrations more accurately than existing immunofixation methods [5]. It is being used in routine laboratories in the United States and Germany and at specialist centres in the UK in the diagnosis and management of patients with myeloma [6], suggesting the technique could readily be made available to clinicians. It has also been used to monitor the response to chemotherapy in a series of patients with systemic AL amyloidosis [7]. A reduction in free light-chain concentrations correlated with an increased probability of survival.

In this case, the development of the nephrotic syndrome and renal impairment occurred secondary to LCDD in the absence of an identifiable underlying B cell clonal disorder. Treatment with VAMP chemotherapy resulted in a significant reduction in circulating light-chain levels and the kappa:lambda ratio. This was monitored using the new, sensitive Freelite immunoassay. This was associated with a reduction in the degree of proteinuria to the non-nephrotic range and an improvement in renal function. A reduction in kappa:lambda ratio has been shown to have prognostic significance in multiple myeloma [8].

The exact mechanism by which renal function and proteinuria improved following chemotherapy is not clear. A further renal biopsy was not considered appropriate as the patient was clinically improving, so it is not possible to say whether there was resolution of the pre-existing structural damage or a reduction in light-chain deposition within the kidney as a result of the chemotherapy. However, the former seems unlikely. The rapidity with which the renal function improved suggests that the response following chemotherapy was, at least in part, a functional improvement possibly due to a reduction in an ongoing toxic insult to the kidney.

This is the first case to demonstrate a direct relationship between the measurement of the precursor protein in the serum and renal function in LCDD. Reducing the circulating light chains and, therefore, the amount of light-chain deposits in the kidney is able to significantly improve renal function and delay the need for renal replacement therapy. This has significance in the future monitoring and treatment

of patients with LCDD in the kidney and implications for the importance of therapy aimed at reducing circulating levels of light chains.

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Conflict of interest statement. None declared.

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