Light chains and the kidney

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SUMMARY Five cases of renal impairment caused by the deposition of light chains in the kidney in association with various immunoproliferative disorders are reported. Light microscopy, immunohistochemistry, and electron microscopy were undertaken and different clinical courses were studied, resulting in variable influences of treatment. Light chain deposition is an important cause of renal impairment and requires special histological techniques for its recognition.

One of the mechanisms implicated in the development of renal impairment in myeloma is toxicity to the kidney caused by myeloma proteins.¹ It is now apparent that immunoglobulin light chains may become deposited in and damage the kidney, even in the absence of myeloma, and the terms light chain deposition disease² and light chain nephropathy³ have been used to describe this process. It is unclear why light chains, which are normally freely filtered at the glomerulus and catabolised in the proximal tubule,⁴ should become nephrotoxic. The production of excess or abnormal light chains, although implicated in many cases, is not always evident. The absence of an underlying immunoproliferative disorder or of monoclonal light chains in the plasma or urine does not exclude the diagnosis,⁵ which can only be made with confidence on histological examination of renal tissue. Various histopathological abnormalities have been recognised,⁶ with the identification of light chains by immunohistochemistry being the diagnostic feature.

We report five cases in which renal impairment was associated with the deposition of immunoglobulin light chains in the kidney.

Methods

Percutaneous needle biopsy specimens were studied by light, electron, and immunofluorescence microscopy. Samples for light microscopy were fixed in 10% buffered formal saline and embedded in paraffin. Sections were cut at 2 to 3 microns and stained with haematoxylin and eosin, periodic acid Schiff, Masson's trichrome, periodic acid silver methenamine and Congo red. In addition, sections were stained for IgG, IgA, IgM and κ and λ light chains using the immunoperoxidase technique. Samples for

immunofluorescence microscopy were snap frozen in liquid nitrogen and stored at -90°C . Cryostat sections were stained with fluorescein labelled antisera against human immunoglobulins G, A, M (heavy chain specific), κ and λ light chains C₃, C_{1q}, and fibrinogen by standard methods. For electron microscopy, specimens were fixed in cold 2.5% glutaraldehyde, postfixed in 1% osmic acid, dehydrated in graded alcohols, and embedded in Epon 812. Thin sections were double stained with uranyl acetate and lead citrate. Plasma and urine free light chain values were measured by immunoprecipitation techniques and expressed as g/l with reference to grams of polyclonal standard.

Case histories

CASE 1

In September 1982 a 65 year old storeman was found to be anaemic and to have renal impairment. There was a family history of anaemia. Haemoglobin was 6.7 mg/100 ml with an elliptocytosis on blood film; the white cell count was $10.4 \times 10^9/\text{l}$, platelet count $376 \times 10^9/\text{l}$, and erythrocyte sedimentation rate 27 mm/first hour. Red cell fragility was increased. Bone marrow was cellular with large numbers of elliptocytes and microspherocytes. Plasma cells constituted 8% of the population. Urea was 15.8 mmol/l (94.8 mg/100 ml) and creatinine 412 $\mu\text{mol/l}$ (4.6 mg/100 ml). Twenty four hour urine volume was 1.57 l with a creatinine clearance of 14 ml/minute and a protein loss of 4.3 g. Total protein concentration was 71 g/l, albumin 41 g/l, and calcium 2.26 mmol/l (10.4 mg/100 ml).

Renal biopsy findings (figs 1 and 2) showed 18 glomeruli, of which six were totally sclerosed. The rest were all abnormal and had a lobular pattern with segmental or global nodular expansion of the mesangium. The mesangial expansion was predom-

Fig 1 Nodular mesangial staining for κ chains (Immunoperoxidase stain.) $\times 500$.

inantly of the matrix with either very little or no evidence of cellular increase. Most of the capillary loops peripheral to the mesangial nodules had widely patent lumina with thin unremarkable capillary walls. Tubules showed foci of atrophy with pronounced thickening and lamination of the basement membrane, especially with the periodic acid Schiff stain. Immunoperoxidase stains showed intense positive staining of the mesangial nodules, glomerular capillary walls, and tubular basement membranes for κ light chains and negative staining for λ . Electron microscopy showed that there were large coarsely granular electron dense deposits within the expanded mesangium and finely granular continuous band like deposits in the capillary and tubular basement membranes. Special stains for amyloid were negative.

In view of these renal biopsy findings repeat bone marrow examination and a search for a plasma or urinary monoclonal band were performed. Repeat bone marrow examination showed that although plasma cell numbers were not increased, most stained heavily for κ light chains. No monoclonal band was

Fig 2 Thickened laminated tubular basement membrane staining heavily for κ chains (Immunoperoxidase stain.) $\times 500$.

found in plasma. Urinary free light chain estimations showed 0 g/l of κ chain and 0.08 g/l of λ chain. No monoclonal bands were found, even after concentration of urine. These findings, although unusual, were not considered to refute the diagnosis of κ chain nephropathy.

By October 1983 creatinine clearance had fallen to 4.8 ml/minute. Bone marrow appearances were unchanged and monoclonal light chains remained absent from plasma and urine, but in view of his progressing renal failure he was started on cyclophosphamide to try to reduce any κ light chain production. Despite this, creatinine clearance fell to 1.18 ml/minute by December 1983 when haemodialysis was started. Cyclophosphamide was stopped in April 1984 because of leucopenia, his white cell count returning to normal after treatment was stopped. In January 1985 routine skeletal survey showed lytic lesions in both humeri, femore, and the pelvis, and bone marrow examination showed increased numbers of abnormal plasma cells consistent with myeloma. Treatment with melphalan was started.

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CASE 2

An aeroplane designer was found to have lymphocytosis on routine blood count in 1975 at the age of 45. Chronic lymphocytic leukaemia was diagnosed on bone marrow examination. By 1977 total white cell count had risen to $51.0 \times 10^9/l$ with 93% lymphocytes, and treatment with chlorambucil was started. Renal impairment was noted in September 1983 when urea was 18.1 mmol/l (108.6 mg/100 ml) and creatinine $340 \mu\text{mol/l}$ (3.8 mg/100 ml). Twenty four hour urinary volume was $2.24 l$ with a creatinine clearance of 12.2 ml/minute . Haemoglobin was 10.5 mg/100 ml , white cell count $9.4 \times 10^9/l$ (80% lymphocytes), platelet count $166 \times 10^9/l$ and erythrocyte sedimentation rate 39 mm/first hour ; chlorambucil was stopped. Total protein was 52 g/l , albumin 26 g/l , and calcium 2.01 mmol/l (8.0 mg/100 ml). Plasma protein electrophoresis showed a very weak band of IgG κ light chain.

Renal biopsy findings (figs 3 and 4) showed two interrelated morphological abnormalities. Fourteen

of 20 glomeruli were totally sclerosed. The rest showed a spectrum of changes including focal segmental scarring, widening of glomerular capillary walls secondary to mesangial interposition, and occasional hyaline insudative lesions within the thickened walls. Proximal tubules were noticeably atrophic with thickening and lamination of the basement membrane. Immunohistochemical staining showed intense staining of focal capillary walls and thickened tubular basement membranes for IgG and κ light chains. These glomerular and tubular changes were indicative of a light chain nephropathy.

There was also a monoclonal infiltration of lymphocytes, positive for IgG κ only, compatible with infiltration by a malignant lymphoid neoplasm. Electron microscopy (fig 4) showed polygonal crystalline structures within most of these lymphocytes, which most probably represented immune proteins. Amyloid was not identified. Renal function initially continued to deteriorate and haemodialysis was required for several

Fig 3 Dense interstitial infiltrate of lymphoid cells staining for κ chains (Immunoperoxidase stain.) $\times 200$.

Fig 4 Electron micrograph of interstitial lymphocyte containing cytoplasmic crystalline structures. $\times 27\,000$. (Sections for electron microscopy were obtained by reprocessing part of paraffin block).

months. Intermittent treatment with chlorambucil was continued and renal function improved sufficiently for him to have become independent of dialysis for the following 16 months.

CASE 3

A 54 year old milkman became confused and suffered two grand mal fits. On admission to hospital he was febrile with signs of meningeal irritation but no focal neurological signs. Haemoglobin was 9.6 mg/100 ml, white cell count $6.7 \times 10^9/l$, platelet count $119 \times 10^9/l$ and erythrocyte sedimentation rate 23 mm/first hour. Plasma sodium was 115 mmol/l, urea 4.8 mmol/l (28.8 mg/100 ml), and creatinine 105 $\mu\text{mol/l}$ (1.2 mg/100 ml). His 24 hour urinary volume was 6.24 l with a sodium loss of 1080 mmol, protein leak of 1.2 g, and creatinine clearance of 132 ml/minute. A brain computed tomography scan yielded normal results, but examination of the cerebrospinal fluid showed lymphocytic meningitis. He was treated with Acyclovir and made a good recovery. Herpes simplex virus complement fixation titres

rose from less than 8 to 32 over the next two weeks. Total serum protein was found to be 119 g/l with a serum albumin of 23 g/l and calcium 2.0 mmol/l (8.0 mg/100 ml). Free IgG λ light chains were found in plasma at a concentration of 60.6 g/l and in urine at a concentration of 1.6 g/l. An examination of the bone marrow showed abnormal plasma cell proliferation consistent with myeloma. Renal biopsy (fig 5) showed hyaline eosinophilic casts within distal tubules, surrounded by syncytial giant cells, consistent with a diagnosis of "myeloma kidney". Stains for amyloid were negative. During treatment with melphalan and later cyclophosphamide and steroids, urinary free light chains became undetectable and plasma free light chain concentration fell to 55 g/l, but the urinary sodium leak and hyponatraemia persisted. Creatinine clearance remained normal throughout. He became septicaemic and died six months after diagnosis.

At necropsy there was extensive replacement of the bone marrow and spleen by myeloma cells. At the oesophagogastric junction a deposit of tumour was present within the submucosa with ulceration of the overlying mucosa. The kidneys were pale and of normal size and showed microscopic abnormalities very similar to those in the renal biopsy specimen, with hard eosinophilic tubular casts surrounded by syncytial giant cells. There was no evidence of infiltration by myeloma cells and special stains for amyloid were negative. The lungs were extremely heavy and both lower lobes had patchy consolidation indicative of bronchopneumonia. The alveolar spaces contained a fibrinous and haemorrhagic exudate with many inflammatory cells. Macrophages predominated, with aggregates of plasma cells and a few lymphocytes and polymorphs. The changes were characteristic of an acute pneumonia in a severely neutropenic patient where the predominant cellular response consists of macrophages.

Fig 5 Renal tubule containing typical myeloma cast with syncytial cellular reaction. $\times 500$.

CASE 4

A 72 year old woman developed a rash and diarrhoea in December 1984 while taking mefenamic acid for backache. She had a generalised macular rash and tenderness over the lower thoracic spine. Haemoglobin was 10.6 mg/100 ml, white cell count $5.9 \times 10^9/l$, platelet count $184 \times 10^9/l$ and erythrocyte sedimentation rate 17 mm/first hour. She was found to be in renal failure with a urea of 55.1 mmol/l (331.2 mg/100 ml) and creatinine 1500 $\mu\text{mol/l}$ (17.0 mg/100 ml). Twenty four hour urine volume was 0.31 l with a creatinine clearance of 0.6 ml/minute and protein loss of 0.2 g. Total protein was 48 g/l, albumin 21 g/l, and calcium 2.07 mmol/l (8.3 mg/100 ml). Radiographs of the thoracic spine showed collapse of the eleventh thoracic vertebra.

Renal biopsy was performed to ascertain the cause

Fig 6 Interstitial oedema and tubular epithelial cell degeneration and necrosis. $\times 500$.

of her renal failure. The histological abnormalities were twofold (fig 6). Firstly, there were tubular casts with giant cell reaction indicating that the patient had unsuspected myeloma. Stains for amyloid were negative. Secondly, there was evidence of proximal tubular epithelial cell degeneration and necrosis consistent with mefenamic acid induced ischaemic damage. No monoclonal band was found in plasma, but an IgM λ paraprotein was present in the urine. Urinary free λ light chain concentration was 2.5 g/l. Abnormal plasma cell proliferation was found on bone marrow examination.

Mefenamic acid was stopped and treatment with melphalan and steroids and intermittent haemodialysis was started. Renal function gradually improved allowing haemodialysis to be discontinued after four weeks when creatinine clearance had risen to 5.8 ml/minute. A year after presentation her urinary paraprotein persisted despite continued treatment with melphalan and steroids but creatinine clearance was 33 ml/minute with a 24 hour urinary protein loss of 0.2 g.

CASE 5

A 50 year old personnel officer presented in May 1985 with a vasculitic rash on her legs. The rash had been present for five years but had become more noticeable with areas of ulceration over the preceding few months. Haemoglobin was 9.7 mg/100 ml with a white cell count of $13.0 \times 10^9/l$, platelet count of $218 \times 10^9/l$ and erythrocyte sedimentation rate 77 mm/hour. Urea and creatinine concentrations were increased to 7.8 mmol/l (46.9 mg/100 ml) and 278 $\mu\text{mol/l}$ (3.1 mg/100 ml), respectively, with a creatinine clearance of 33 ml/minute. Total protein concentration was 66 g/l, albumin 39 g/l, and calcium 2.18 mmol/l (8.7 mg/100 ml). An IgM cryoglobulin was found in her plasma and an IgM κ paraprotein in her urine. Urinary free light chain estimations showed 2.8 g/l of κ chains and 0.3 g/l of λ chains.

A skin biopsy specimen showed vasculitis with no specific immunoglobulin deposition, and bone marrow aspirate showed a sparse diffuse infiltrate of lymphoplasmacytoid cells. A renal biopsy showed nodular focal interstitial infiltrates of plasmacytoid lymphocytes, tubular atrophy, and casts. There was no evidence of a cellular reaction to the casts. Stains for amyloid were negative, but immunohistochemistry showed that most of the lymphocytes had stained for IgM κ . Treatment with melphalan was started with no further deterioration in renal function.

Discussion

The deposition of immunoglobulin light chains in the kidney is well recognised as a feature of various immunoproliferative disorders, the most common of which is myeloma. It is now becoming increasingly recognised that patients may present with the stigmata of a paraprotein nephropathy without having any other clinical, haematological, or biochemical evidence of an immunoproliferative disorder.⁷ We have presented here five cases with a range of immunoproliferative disorders, all with different clinical problems at presentation and a spectrum of abnormalities on renal biopsy. Case 1 presented with anaemia and renal impairment, case 2 with chronic lymphocytic leukaemia, case 3 with viral meningitis, case 4 with renal failure and evidence of a hypersensitivity reaction to mefenamic acid, and case 5 with a cutaneous vasculitis. Overt myeloma was present in cases 3 and 4, an abnormal lymphoplasmacytoid cell proliferation in case 5, and chronic lymphocytic leukaemia in case 2. In case 1 no evidence of an immunoproliferative disorder was found at presentation, with light chain deposition occurring in the kidney despite monoclonal light chains being absent from both plasma and urine. Classical myeloma developed

two years after presentation, emphasising the need for careful haematological follow up in cases in which the underlying source of light chain production is not obvious.

In the cases we have described the histological appearances differed from patient to patient. Thus deposition of light chains may occur in the glomerular basement membrane, in the mesangium with accompanying glomerular nodules, in the tubular basement

membrane and as tubular casts. Tables 1–3 summarise the findings on light microscopy, immunohistochemistry, and electron microscopy, respectively. The nodular glomerulosclerosis of κ chain nephropathy is quite similar to the light microscopic abnormalities seen in nodular diabetic glomerulosclerosis, renal amyloid, and mesangio-capillary glomerulonephritis type I. The nodules in these conditions are due to expansion of the

Table 1 *Light microscopic findings on renal biopsy*

Case No	Glomeruli			Tubules	Interstitial	Blood vessels	Other
	Capillary wall	Mesangium	Other				
1	Normal	PAS positive non-argyrophilic mesangial nodules ++	30% totally sclerosed	Tubular atrophy ++ Tubular basement membrane thickening ++ Casts +	Fibrosis +	Arteriolar sclerosis +	
2	Thickening with interposition Insudative lesions +	Matrical increase +	75% totally sclerosed	Tubular atrophy +++ Tubular basement membrane thickening ++ Casts ++	Fibrosis + Lymphocytes in large aggregates ++	Arteriolar sclerosis ++	Lymphocytes in perirenal tissues ++
3	Normal	Focal segmental cellular increase +	Mini epithelial crescents +	Distal tubular and collecting duct casts with syncytial giant cells ++	Lymphocytes + Plasma cells +		
4	Normal	Cellular increase +		Proximal tubular degeneration and necrosis ++ Distal tubular casts with syncytial giant cells +	Oedema ++ Lymphocytes, plasma cells and eosinophils +	Peritubular capillary dilatation ++ Arteriolar sclerosis +	
5	Normal	Normal	Epithelial proliferation +	Tubular atrophy ++ Tubular hyaline casts ++ No giant cell reaction	Nodular infiltrates plasmacytoid lymphocytes ++	Arteriolar sclerosis +	

Staining: + mild; ++ moderate; +++ extensive.

Table 2 *Immunohistochemistry on renal biopsy*

Case No	Glomeruli		Tubules		Other
1	IgG	focal, granular capillary walls ++	IgG	tubular basement membrane +	
	κ	focal, granular capillary walls +++ mesangial nodules +++	κ	tubular basement membrane +++ casts +	
2	IgG	focal capillary walls ++	IgG	tubular basement membrane ++	IgG interstitial lymphocytes +++
	κ	focal capillary walls ++	κ	tubular basement membrane ++	κ interstitial lymphocytes +++ IgA, IgM, λ negative
3	Negative		IgG	tubular basement membrane +++	
4	IgG	focal, linear capillary walls +			
	λ	capillary walls +++	λ	casts +++ reabsorption droplets +++	
5	Negative		Negative		IgM – 75% interstitial lymphocytes ++ κ – 75% interstitial lymphocytes ++ IgG, IgA and λ < 10% interstitial lymphocytes +

Staining: + minimal staining; ++ moderate staining; +++ heavy staining.

Table 3 *Electron microscopy on renal biopsy*

Case No	Glomeruli	Tubules	Other
1	Focal obliteration of epithelial cell foot processes Large, granular, electron dense deposits in mesangium + linear dense band within glomerular basement membrane	Finely granular almost continuous dense deposits in some tubular basement membrane	
2	Focal obliteration of foot processes, mesangial cell interposition + mesangial matrical increase Dense, finely fibrillar deposits within glomerular basement membrane of some capillary loops	Non-specific changes only	Fibrillar deposits in media of arteriole Large lymphocytes in interstitium with prominent irregular nuclei and cytoplasm containing polygonal crystalline structures with a lattice like configuration
3	No significant abnormality except for mesangial matrical increase	No significant abnormality	
4	Diffuse obliteration of foot processes and moderate increase in mesangial matrix	Tubular casts with fibrillar structure	
5	Focal obliteration of foot processes with glomerular basement membrane thickening and mild mesangial matrical increase	No significant abnormality	Lymphocytes in interstitium

mesangium by increased matrical substance, as occurs in diabetes and mesangiocapillary glomerulonephritis, or deposition of abnormal proteins like amyloid or κ light chains. Although the nodules tend to be relatively hypocellular or acellular in κ chain nephropathy, they can, on occasion, be proliferative and hypercellular and bear a striking resemblance to early mesangiocapillary glomerulonephritis. An important feature that is helpful in the light microscopic differential diagnosis is the extensive mesangial interposition and double contour of glomerular capillary loops in mesangiocapillary glomerulonephritis. Immunohistochemistry and electron microscopy would, of course, quite easily differentiate between these two conditions with coarse granular C_3 along peripheral capillary loops, varying numbers of electron dense deposits, and double contour appearance of the capillary basement membrane in mesangiocapillary glomerulonephritis type I, whereas in κ chain nephropathy there would be intense almost exclusive staining for κ chains and electron microscopy would have the characteristic appearances discussed in case 1.

In the differential diagnosis from nodular diabetic glomerular sclerosis the salient points are that, unlike in cases of κ chain nephropathy, the nodules are not diffuse, are generally of variable sizes, and only in a few glomeruli are all the lobules affected. On immunofluorescence microscopy most have linear IgG of glomerular and tubular basement membrane (in the absence of antiglomerular basement membrane antibodies), and the electron microscopic appearance of a regular homogenous increase in

thickness of glomerular capillary basement membrane without deposits is almost unique to diabetes mellitus.

Light chain nephropathy may trap the unwary into diagnosing membranoproliferative glomerulonephritis, diabetic glomerulosclerosis, or renal amyloid. Some of the cases of prediabetic diabetic glomerulosclerosis reported in patients without any evidence of diabetes mellitus may well have been unsuspected cases of κ chain nephropathy.

Special stains for amyloid were negative in all of the cases described, and it is important to differentiate amyloidosis from the form of light chain deposition reported here. Although amyloidosis is associated with the deposition in various organs, including the kidney, of immunoglobulin derived material (most commonly λ light chains),⁸ its presence depends on the formation by its protein constituents of a β pleated fibrillar structure. It is this β pleated fibrillar configuration that binds with Congo red dye, and this was absent in the cases described. The reason why light chains should in some cases form amyloid deposits but in others become deposited in the patterns described here is thought to relate to variations in their structure and physicochemical properties.⁹

The synthesis of light chains, which are abnormal in either size or structure, seems to be the major factor in determining their nephrotoxicity,¹⁰ and the isoelectric point of the light chain has been proposed as a particularly important determinant.¹¹ Thus variations in the isoelectric point may influence filtration though the negatively charged glomerular basement

membrane or precipitation in casts with the anionic Tamm-Horsfall mucoprotein. Similarities between the glomerular lesions described in case 1 and those found in diabetic patients have led to the suggestion that glycosylation of light chains may be important.⁵

The clinical diagnosis of renal light chain deposition can be challenging as the clinical features vary according to the different patterns of deposition within the kidney. Renal failure and proteinuria are particularly associated with glomerular deposition, and failure of concentrating powers with tubular deposition. The recognition of the disorder is clearly important as treatment may be effective. In cases where a well recognised immunoproliferative disorder is present treatment can be directed towards this. The indication for and methods of treatment become less clear, however, when an underlying immunoproliferative disorder cannot be identified.²

All patients in our series received treatment with alkylating agents, and follow up has ranged from six months to three years. Renal function improved after treatment in cases 2 and 4, although a potentially reversible interstitial nephritis due to mefenamic acid accounted for some of the renal impairment in case 4.¹² Renal function has remained stable in case 5, with serum creatinine concentration at 300 $\mu\text{mol/l}$ (3.4 mg/100 ml). In case 3 the sodium leak persisted and the patient died three months after presentation as a consequence of myeloma and immunosuppression, and in case 1 renal failure progressed despite treatment.

Deposition of light chains in the kidney is an important cause of renal disease that will only be detected if the diagnosis is suspected and renal biopsy tissue examined using special histological techniques. It should be considered in all cases of renal impairment in which the cause is not obvious.

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