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Kappa light chain nephropathy

A pathologic study

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Summary. Percutaneous renal biopsies from 4 patients with clinically unsuspected kappa light chain nephropathy were studied using light, immunofluorescence, and electron microscopy. The diagnosis in each case was established by demonstrating monoclonal kappa light chain deposits in basement membranes and basement membrane-like structures of glomeruli, tubules, and blood vessels by immunofluorescence microscopy. Characteristic electron dense deposits occurred in every case but the intensity and distribution of electron densitites did not correlate with the immunofluorescence findings. When light chain aggregation occurred, as evidenced by the distribution of electron dense deposits, it was proportional to the amount of basement membrane-like material as if these immunoglobulins had a particular affinity for structures chemically related to basement membranes. Although active tubulointerstitial lesions were prominent in all biopsies, there was considerable variation in glomerular pathology with only 1 case exhibiting the typical nodular glomerulosclerosis. Correlation of the light, immunofluorescence, and electron microscopic findings in these cases suggests that the pathogenesis of kappa light chain nephropathy is related to light chain nephrotoxicity directed to basement membrane-like structures with subsequent alterations in hemodynamics and structural renal damage.

Key words: Light chain nephropathy – Light chain deposition – Multiple myeloma – Kappa light chains – Myeloma kidney

Introduction

The kidney is often involved in patients with plasma cell dyscrasias and certain lymphoproliferative disorders [5]. The most common morphological changes result from the accumulation of free light chains either in the form of myeloma kidney (cast nephropathy) or amyloidosis [4, 17, 20, 27]. In recent years, increasing attention has focused on a rare pathological variant of renal disease in these patients wherein monoclonal light chains, usually of the kappa type, are selectively deposited along the basement membranes of glomeruli, tubules, and blood vessels as well as along chemically related structures such as mesangial matrix and the pericellular basement membrane-like material of vascular smooth muscle cells [7, 8, 9, 22]. Although immunofluorescence with antibodies to free kappa light chains yields a characteristic microscopic pattern, the histologic changes vary widely and a complete understanding of the pathology of kappa light chain nephropathy requires immunofluorescence and light microscopy in conjunction with ultrastructural studies. [3, 6, 12, 19, 24]. Most authors have emphasized the light microscopic features of kappa light chain nephropathy and detailed electron microscopic analyses correlated with immunofluorescence have rarely been reported [21, 23]. The following is a complete description of 4 cases of kappa light chain nephropathy. It is our purpose to correlate the light microscopic findings with immunofluorescence and electron microscopic studies and to discuss the possible implications of these observations for the pathogenesis of the disease.

Materials and methods

All cases of kappa light chain nephropathy evaluated in the Diagnostic Nephropathology Reference Laboratory at Baptist Memorial Hospital, Memphis, Tennessee, from 1980 to 1985 were included. Two [2] cores of renal tissue were received in each case and processed according to standard methods in our laboratory [16]. Tissue for light microscopy was fixed in Carson's buffered formalin, embedded in glycol methacrylate plastic, sectioned at 2.5 microns and stained with hematoxylin and

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Table 1. Summary of clinical data

Patient	Age, sex	Serum creatinine/ BUN (mg/dl)	Urinary protein (g/24 h)	SPEP/ SIEP	UIEP	Bone marrow	Other findings	Course
1	55, F	10.5/119	1.3	Normal	Kappa light chain spike	50% plasma cells	Osteolytic bone lesions	Alive, 1 year renal failure
2	36, M	10 /100	0.27	↓IgG	Trace monoclonal kappa light chains	20% abnormal plasma cells	Multiorgan involvement	Alive, $2^1/_2$ years renal failure
3	71, M	10.6/101	2.3	↓IgG	Normal	10–15% atypical plasma cells	–	Alive, $1^1/_2$ years renal failure
4	57, M	11.5/101	2.3	Normal	Not done	100% plasma cells	Multiorgan involvement	Dead, 4 weeks Light chain myeloma

Abbreviations: SPEP: Serum protein electrophoresis; SIEP: Serum immunoelectrophoresis; UIEP: Urine immunoelectrophoresis

Table 2. Morphologic findings

	Case 1	Case 2	Case 3	Case 4
*Tubulointerstitial lesions**				
Fibrosis	++	++	+++	+++
Tubular injury	+++	+++	+++	++
TBM thickening	+	+	++	++
Refractile casts	+	+	+	+
IM-kappa deposits in TBMs	Linear	Linear	Linear	Linear
EM-dense deposits in TBMs	Variable	Variable	Variable	Variable
*Glomerular lesions***				
Mesangial widening	–	+	+	+
Mesangial nodules	–	–	+	–
Mesangial globules	–	+	–	–
Capillary wall thickening	–	+	+	+
IM-kappa deposits:				
GBM	Linear	Linear	Linear	Linear
Mesangium	+	+	+	+
BC	Linear	Linear	Linear	Linear
EM-kappa light chain deposits:				
GBM	Inconspicuous	+	Inconspicuous	Inconspicuous
Mesangium	+	+	+	+

Abbreviations and symbols. TBMs = tubular basement membrane; GBM = glomerular basement membrane; BC = Bowman's capsule; IM = immunofluorescence microscopy; EM = electron microscopy;

* + = rare; ++ = prominent; +++ = extensive

** + = present; – = absent

eosin (H&E), periodic acid-Schiff (PAS), and periodic acid methenamine silver (PAM). A Congo red stain was examined under polarized light for amyloid in each case. Tissue for electron microscopy was fixed in 2% glutaraldehyde, post-fixed in 1% osmium tetroxide, embedded in Spurr plastic, sectioned at 0.08 microns, stained with uranyl acetate and lead citrate, and examined in a Zeiss 109 electron microscope. Tissue for immunofluorescence was covered with OCT embedding medium, snap frozen in liquid nitrogen, sectioned at 4 microns, and reacted with monospecific, commercially prepared fluorescein conjugated antisera to human IgG, IgA, IgM, free kappa and lambda light chains, C3, C1q, properdin, fibrin reactive products, and alpha$_2$ globulin.

Of the 4 patients, 3 were male and 1 female, ranging in age from 36 to 71 years (Table 1). All had been hospitalized with signs and symptoms of renal failure varying in duration from several weeks to 1 year. All patients had proteinuria without qualitative Bence Jones reactions. Kidney size measured by ultrasound examination in 3 individuals was normal.

Results

At the time of renal biopsy, no patients had clinical or laboratory findings indicative of plasma cell dyscrasia although subsequent evaluations revealed significant plasmacytosis in the bone marrow of every individual. In addition, patients 1 and 2 had small amounts of free kappa light chains demonstrated by immunoelectrophoresis of their

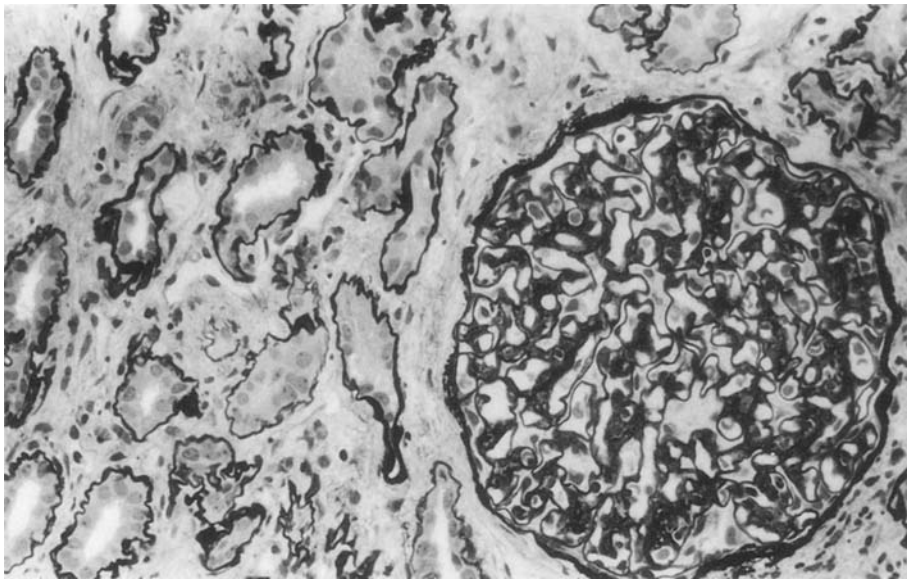

Fig. 1. Focal mild increase in mesangial matrix is present in the glomerulus. There is moderate interstitial fibrosis, widespread tubular degeneration, and wrinkling or focal loss of the tubular basement membranes. (PAM ×300)

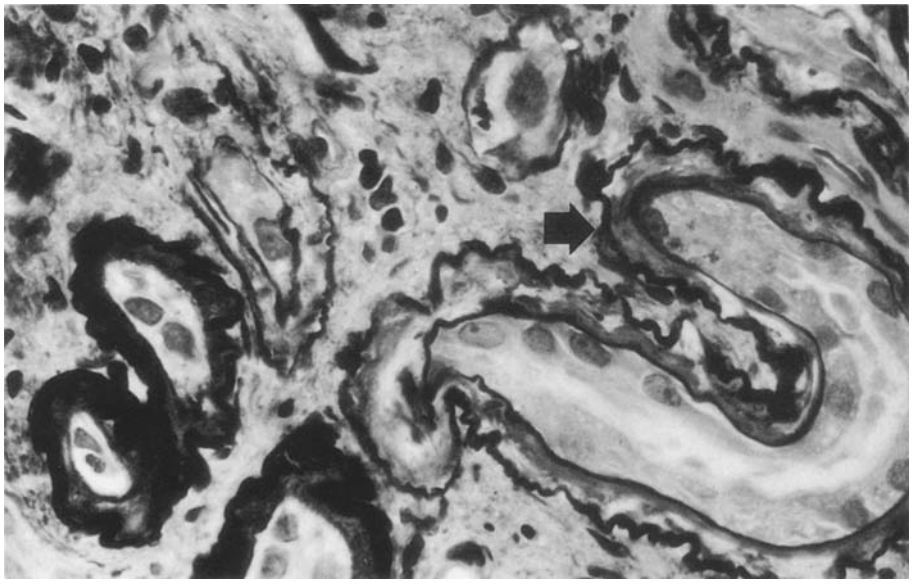

Fig. 2. Non-argyrophilic deposits (*arrow*) are present between layers of tubular basement membranes of atrophic tubules giving a "double contour pattern" appearance. (PAM ×768)

urines and multiple organ involvement by light chains was identified in patients 2 and 4. One [1] patient died 4 weeks after biopsy. Autopsy revealed extensive deposits of kappa light chains in multiple organs. The remaining 3 patients are alive with renal failure for periods ranging up to 2.5 years.

Pathology. Biopsies were composed predominantly of renal cortex having 10–80 glomeruli per case. Stains for amyloid were negative. The pertinent pathological findings are summarized in Table 2 but since kappa light chain nephropathy is a rare disease, a more thorough description of the renal changes is perhaps warranted.

Tubulointerstitial lesions. Light microscopically, widespread tubular degeneration and focal tubular dilatation associated with diffuse interstitial fibrosis and variable tubular atrophy were prominent features of every case (Fig. 1). Tubular atrophy was often characterized by the presence of non-argyrophilic circumferential deposits lying between layers of basement membrane material resulting in a double contour pattern to the tubular basement membranes in tissue stained with methenamine silver (Fig. 2). This change corresponded to ribbon-like, eosinophilic, PAS positive thickening of the tubular basement membranes. The predominant tubular changes, however, were non-specific

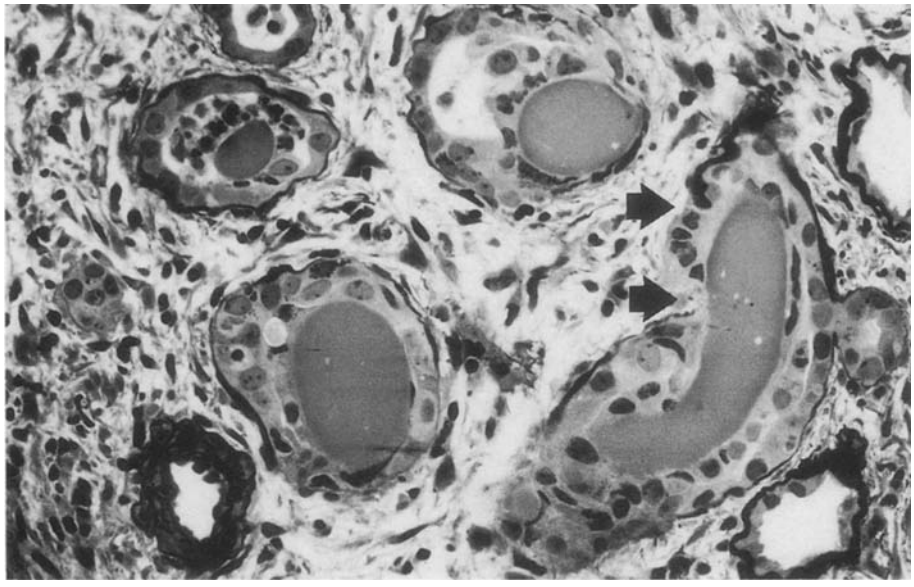

Fig. 3. Tubular injury is characterized by breaks in the basement membranes (*arrows*), flattening and degeneration of the epithelial cells, and focal aggregation of neutrophils in tubular lumina. (PAM ×480)

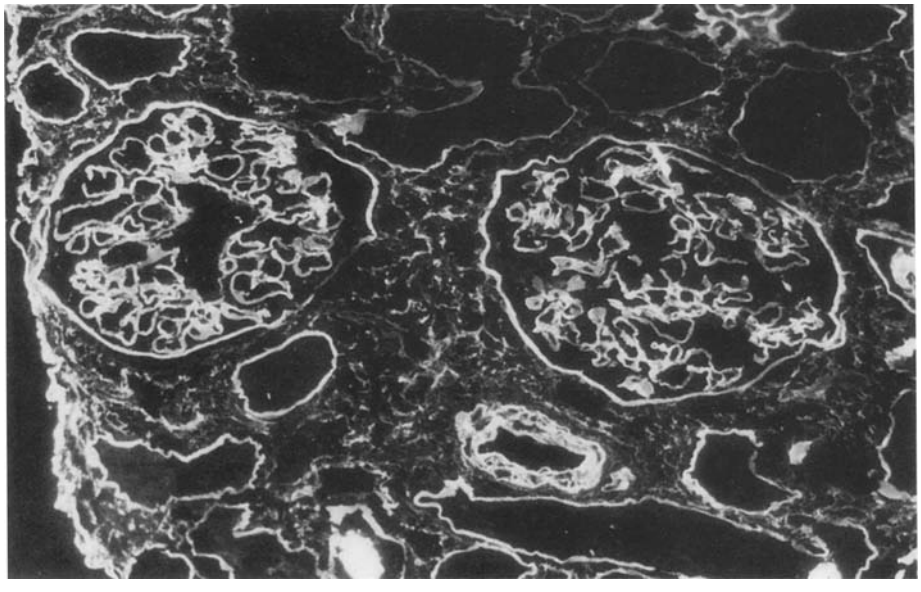

Fig. 4. Linear deposits of kappa light chains are present in the glomeruli, vessels, and tubular basement membranes. Immunofluorescence microscopy (kappa chain antibodies ×320)

basement membrane thickening and wrinkling (Fig. 1). In some areas, active tubular injury characterized by focal tubulorrhexis with disruption of basement membranes and an associated acute and chronic interstitial inflammation was prominent (Fig. 3). Refractile casts occurred in some tubules. Characteristic myeloma casts surrounded by multinucleated giant cells were not identified, however.

Immunofluorescence microscopy revealed a linear pattern of staining along the tubular basement membranes with monospecific antisera for free kappa light chains (Fig. 4). There was negative fluorescence using antisera to human IgG, IgA, IgM, lambda light chains, C3, C1q, fibrin reactive products and alpha$_2$ globulin.

Ultrastructurally, the tubular damage was reflected in loss of proximal tubular brush borders, flattening and exfoliation of the lining cells, and accumulation of cytosegresomes. Crystalline inclusions were not identified. The distribution of electron dense deposits along tubular basement membranes was variable but tended to parallel the amount of basement membrane material present (Figs. 5, 6). Minimal deposition occurred in the thin tubular basement membranes lining relatively intact tubules with preserved basilar infoldings

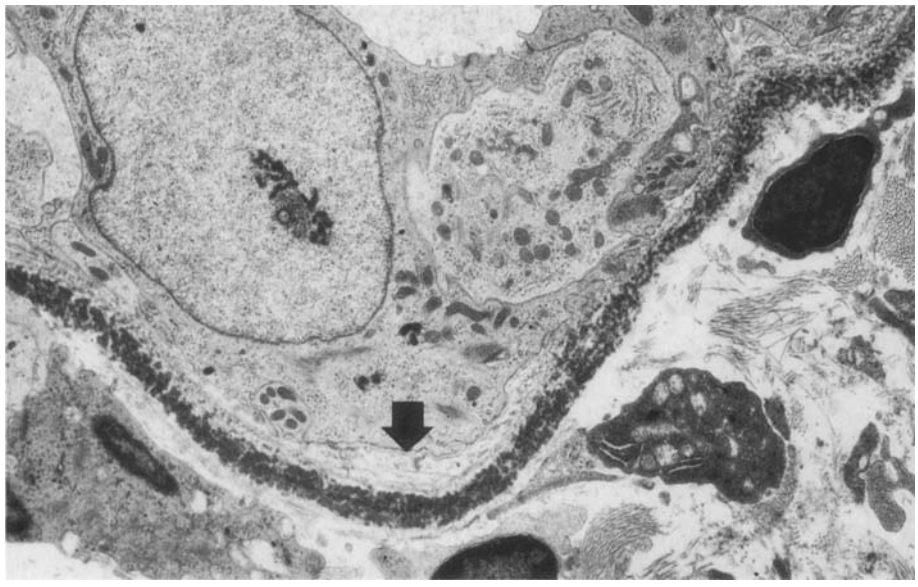

Fig. 5. Well developed kappa light chain deposits are separated from the tubular epithelial cells by thin layers of basement membrane material. (*arrow*) (× 9,000)

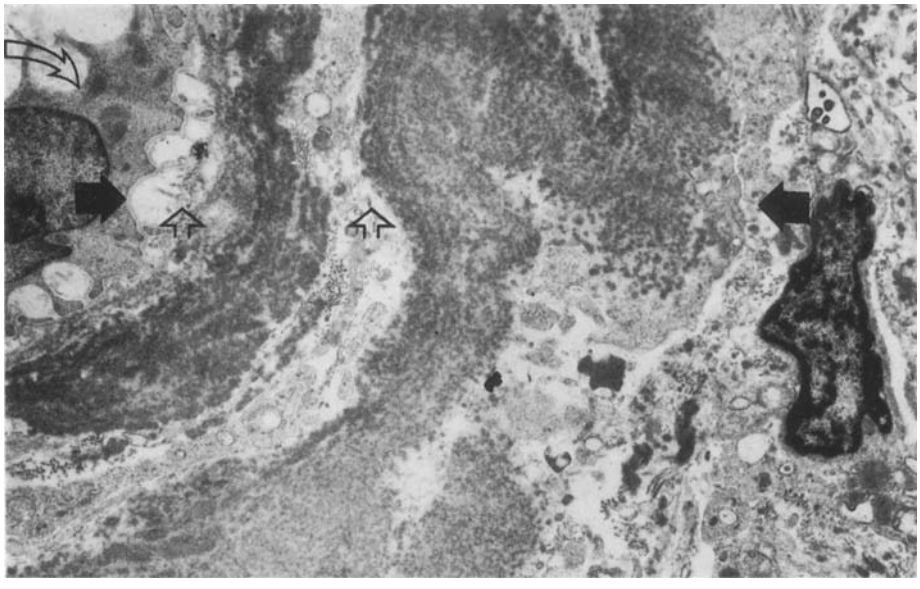

Fig. 6. Multiple layers of markedly thickened tubular basement membrane impregnated with kappa light chain deposits (*between solid arrows*) are separated by lucent layers containing cellular debris and collagen fibrils (*open arrows*). The tubular epithelial cells (*curved arrow*) are atrophic and degenerated. (× 9,000)

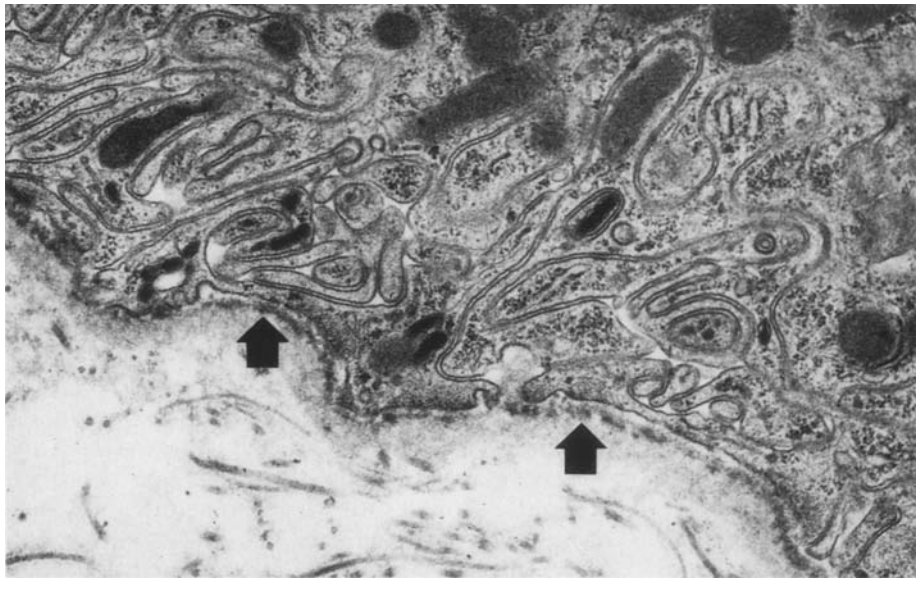

Fig. 7. Inconspicuous kappa light chain deposits (*arrows*) are present internal to the basement membrane of intact tubular epithelial cells with well preserved basilar infoldings. (× 36,000)

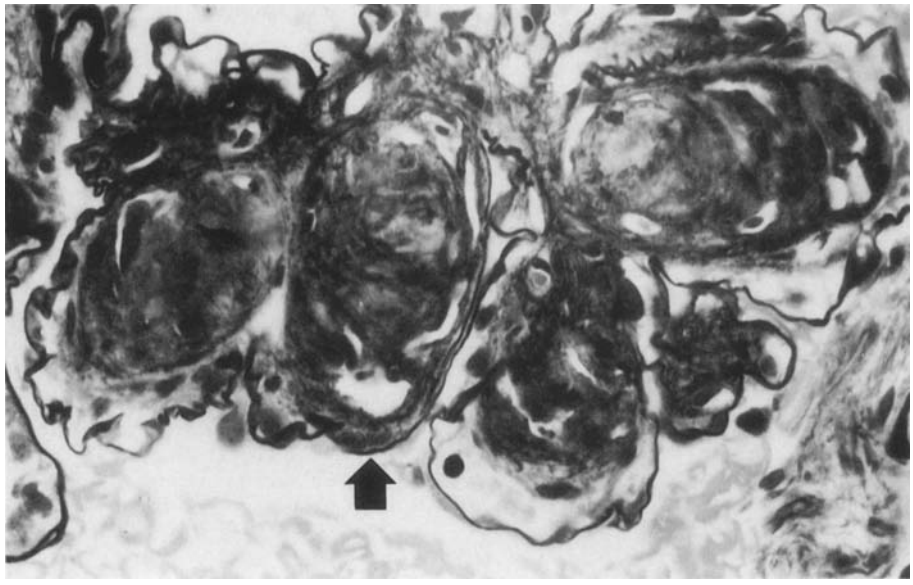

Fig. 8. The hypocellular mesangial nodules have variable argyrophilia. The aneurysmally dilated overlying capillaries have delicate basement membranes. There is marked thickening of the wall of a non-dilated capillary in association with formation of a double contour pattern (*arrow*). (PAM ×768)

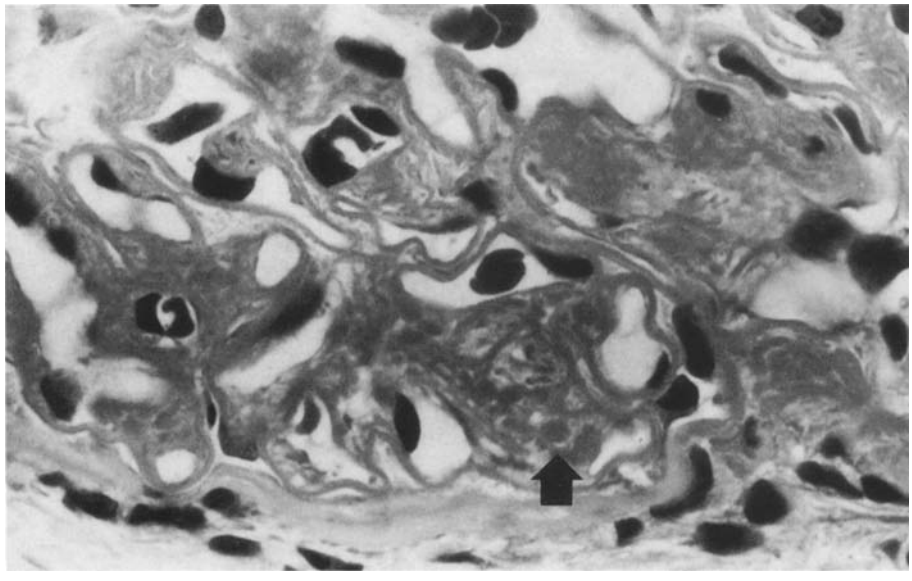

Fig. 9. Eosinophilic globular deposits (*arrow*) are present in the widened mesangial areas. (H&E ×1,208)

(Fig. 7). In some severely damaged tubules, only inconspicuous electron dense deposits were identified along the non-thickened tubular basement membranes.

Vascular lesions. Intimal thickening and mural hyalinization with focal luminal narrowing of arteries and arterioles were identified in every case. The distribution of kappa light chain material, both by immunofluorescence and electron microscopy, was localized to the endothelial basement membrane and the basement membrane-like material surrounding the smooth muscle cells (Fig. 4).

Glomerular lesions. There was considerable variation in glomerular involvement by light microscopy. In case 1, slight increase in mesangial matrix, focal wrinkling of the glomerular basement membranes, and thickening of Bowman's capsules were the only abnormalities (Fig. 1). In contrast, nodular glomerulosclerosis reminiscent of the lesion of diabetic nephropathy occurred in case 3 (Fig. 8). Mesangial widening was prominent in cases 2 and 4. Peculiar eosinophilic, PAS positive, weakly argyrophilic globules were a conspicuous component of mesangial areas in case 2 (Fig. 9). Cellular proliferation was not identified in any case. Focal

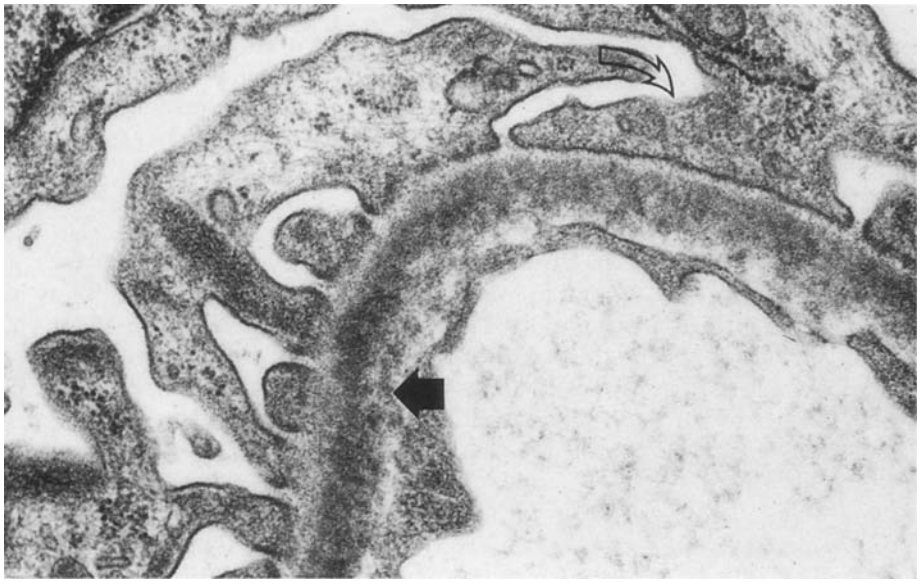

Fig. 10. Discernible but inconspicuous kappa light chain deposits (*arrow*) are present in the lamina densa of a non-thickened capillary wall. There is essentially no abnormality of the visceral epithelial cells (*curved arrow*). (×60,000)

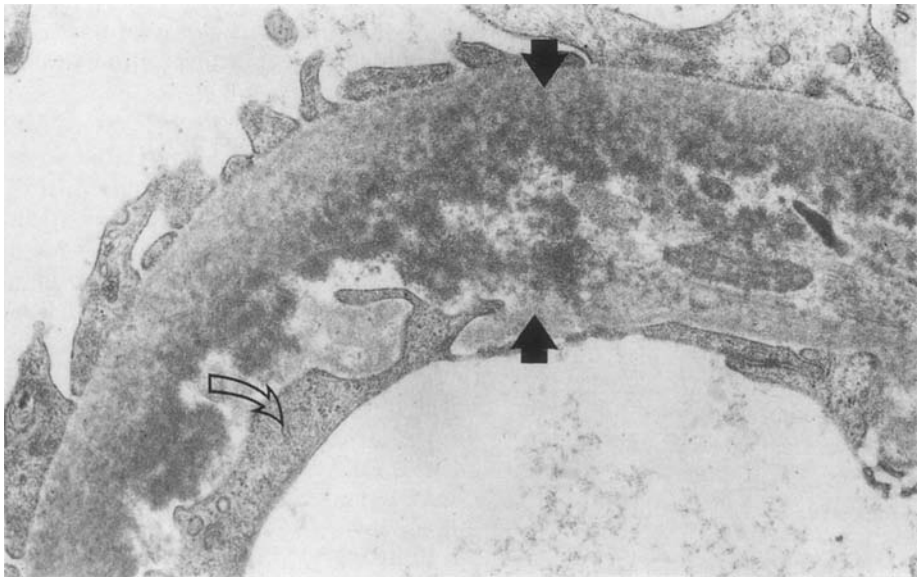

Fig. 11. There is thickening of the capillary wall with accumulation of kappa light chain deposits in the glomerular basement membrane and in the widened subendothelial space (*between arrows*). The endothelial cells have lost their cytoplasmic fenestrations (*curved arrow*). (×36,000)

thickening of the capillary walls with ill-defined double contour patterns on silver staining was present in 3 cases (Fig. 8). Significant glomerular sclerosis indistinguishable from ischemic glomerulosclerosis occurred only in case 4.

There was diffuse linear deposition of kappa light chains in the absence of other serum proteins in every case (Fig. 4). Kappa light chain deposition was identified along the basement membranes of glomeruli and Bowman's capsules as well as in the mesangial regions. The distribution of staining paralleled the amount of basement membrane and/or matrix that was present.

Ultrastructurally, the dense deposits were granular rather than fibrillar and were structurally distinct from amyloid. When inconspicuous amounts of electron dense material were present, they tended to increase the density of the laminae densae (Fig. 10). Large aggregates occurred in widened subendothelial spaces associated with increased basement membrane material and, occasionally, with mesangial cell interposition (Fig. 11). Foot process effacement with microvillous transformation of the visceral epithelial cells was not prominent except in areas of severe glomerular damage. The mesangial deposits were of variable size, forming large globules in case 2 and being intermixed with abundant mesangial matrix in case 3.

Discussion

Kappa light chain nephropathy, when referring to renal deposits of light chain determinants, is an uncommon disease [5, 8, 19, 21, 24]. Although often manifested initially as clinically significant proteinuria associated with renal insufficiency, the disease usually involves multiple organs and tissues. Almost 70% of patients have lymphoproliferative disorders, primarily multiple myeloma [9, 15, 19]. The pathologic diagnosis depends upon identification of kappa light chain determinants by immunofluorescence [7, 8, 9, 22]. These deposits are diffusely distributed along basement membranes of glomeruli, tubules, and blood vessels as well as in mesangial matrix and the basement membrane-like material between vascular smooth muscle cells. Ultrastructurally, peculiar electron dense deposits have been demonstrated in almost every case but the intensity and distribution of the dense deposits does not always correlate with the immunofluorescence [8]. Although superficially resembling amyloid fibrils, the deposits of kappa light chains are ultrastructurally distinct. In fact, the coexistence of kappa light chain nephropathy and amyloidosis of the kidney is extremely rare [13]. Under the light microscope, light chain deposition commonly assumes a glomerular pattern resembling the nodular sclerosis of diabetic nephropathy but many other light microscopic features, including tubular basement membrane thickening, are prominent in most cases [6, 10, 11, 12, 14, 18, 24]. Renal deposition of kappa light chains almost always eventuates in kidney failure regardless of the presence or type of associated hematologic or lymphoproliferative disorders although the disease may be ameliorated if chemotherapy is given early [8, 9, 11].

The clinical features of our cases tend to confirm the relationship between total body load of light chains and severity of symptoms [9]. The pathological findings are at some variance with previously reported cases, however. While most authors have concentrated on the glomerular deposits [6, 10, 11, 14, 19, 23, 24], our cases emphasize the tubulointerstitial changes. These were manifested by moderate to severe interstitial fibrosis and tubular epithelial degeneration associated with focal tubulorrhexis and regeneration in every case. While tubular pathology has been recognized in the cast nephropathy of multiple myeloma [4, 20] and PAS positive deposits in tubular basement membranes have been described [8, 12], it is surprising that lesions of active tubular injury in kappa light chain nephropathy have received little attention. Both light and electron microscopic studies in our cases revealed a spectrum of tubular abnormalities not emphasized in previous reports.

Despite the diffuse distribution of kappa light chains indicated by immunofluorescence, light microscopy revealed a range of tubular and glomerular changes from apparently normal to atrophic. The cases presented here further document the variety of glomerular pathology which can be seen in kappa light chain nephropathy. Nodular mesangial lesions reminiscent of diabetic nephropathy were observed in only 1 of our 4 patients. Among the remainder, light microscopic changes included slight mesangial widening and basement membrane wrinkling, capillary wall thickening in variable association with double contour patterns, and prominent glomerulosclerosis consistent with end stage kidney. In fact, had only light microscopy been available, these cases would have been considered widely dissimilar rather than variations of a single disease.

In contrast to amyloidosis, where large amounts of fibrillar material permeate the glomerular basement membranes and extend into the subepithelial spaces [17, 25, 26], the electron dense deposits of kappa light chains were always associated with basement membrane and chemically related structures and these dense deposits accumulated in direct proportion to the amount of basement membrane material present as if new basement membrane was required as a template for light chain deposition. Thus, relatively larger amounts of light chain deposits were observed in association with laminated tubular basement membranes than among non-thickened membranes. Similarly, thickened glomerular capillary walls with increased basement membrane material contained more abundant granular dense deposits.

The variable *aggregation* of electron dense deposits in contrast to the uniform *deposition* of light chains on immunofluorescence microscopy raises questions regarding the pathogenesis of the renal injury. Is tubular damage the result of the accumulation of light chains in basement membranes with subsequent alterations of transmembranous transport of plasma and/or urine or are kappa light chains toxic to renal structures resulting in physiological damage which only becomes pathologically manifest after the functional alterations have injured the kidney, thus allowing further accumulation of immunoglobulins? The observations in all 4 of our cases of: (1) morphologic evidence for widespread tubular cell injury in the absence of large amounts of light chain aggregates in tubular basement membranes; and (2) aggregation of dense deposits only in areas of increased basement membrane material tend to support the latter pos-

sibility. In fact, the layering of tubular basement membranes around non-argyrophilic deposits may be an important diagnostic feature of kappa light chain nephropathy since this pattern is not characteristic of ischemic tubular atrophy, diabetic nephropathy, or amyloidosis.

It is tempting to speculate that in addition to light chain toxicity, hemodynamic factors, such as those involved in diabetic, focal sclerosing, and reflux nephropathy [1, 2], may be important in kappa light chain deposition, especially since nodular lesions similar to those in diabetic nephropathy are the most common glomerular abnormalities in this disease. Our morphologic observations suggest that the pathology of kappa light chain nephropathy results from a lymphoproliferative neoplasm which produces light chains with inherent nephrotoxicity and affinity for basement membrane-like structures. Deposition of these substances may alter local hemodynamics leading to renal damage which progresses at variable rates depending upon host susceptibility, intercurrent and associated diseases, and perhaps other factors. The resulting pathological changes, though initiated by toxic injury, may resemble those of ischemia and result in variable light microscopic patterns.

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