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Renal Lesions in Multiple Myeloma and Related Disorders

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Summary. **In addition to the so-called myeloma kidney, various types of renal lesions, apparently relating to intrinsic properties of abnormal immunoglobulin products, have been recognized in multiple myeloma and related disorders. Heavy chain deposition disease and heavy-chain-associated amyloidosis are recent newcomers of this group.**

Recognition of morphological features of these lesions is important, since renal manifestations occur often in the absence of overt manifestations of multiple myeloma or other plasma cell dyscrasias. Demonstration of an abnormally predominant deposition of one light chain by immunofluorescence study using anti-kappa and lambda light chain antisera in addition to routine heavy chain staining has been crucial in diagnosing some of these monoclonal light chain-related diseases.

Key words—multiple myeloma, cast nephropathy, amyloidosis, light chain deposition disease, Fanconi syndrome, Crow-Fukase syndrome.

Introduction

Multiple myeloma is a disease caused by neoplastic plasma cells that synthesize abnormal amounts of immunoglobulin or immunoglobulin fragments. These abnormal products induce variable symptoms and clinical courses in addition to common features of neoplastic disease determined by the proliferative capacity of the malignant cells.

Renal manifestations are frequently the first and primary features of the disease, because the kidney is a major target organ for the deposition of such abnormal proteins, and a kidney biopsy may give the first indication of multiple myeloma as an underlying disease.[1,2] Recently, pathologic manifestations of kidney lesions have also been recognized as diverse, this apparently owing to differences in the molecular structures of proteins (Table 1). Kidney lesions due to abnormal immunoglobulins or immunoglobulin fragments are found not only in multiple myeloma but also in other plasma cell dyscrasias including clinically benign conditions.

The purpose of this review is to describe morphological characteristics of various renal lesions and to aid in the interpretation of biopsy or autopsy materials. Essential points of differentiation from renal lesions of other diseases bearing a resemblance in certain renal morphological features and related data of other fields than morphology are also described briefly.

Cast nephropathy

More than 50 percentage of patients with multiple myeloma develop renal failure, and the term myeloma kidney has been used to describe the most common form of renal injury.[3] The classic lesions of myeloma kidney are large intratubular casts surrounded by a cellular reaction, which also give it the name myeloma cast nephropathy.

The casts are predominantly found in the lumina of distal and collecting tubules, and are typically large, dense, often lamellated, and contain numerous fracture lines (Fig. 1). Occasionally rhomboid or needle-shaped crystals are present within the casts. The casts are usually surrounded by various cells including desquamated tubular epithelium, polymorphonuclear leukocytes and large multinucleated giant cells. They are frequently in tubules with discontinuities in their basement membrane.[4] These intratubular casts are accompanied by varying degrees of tubular atrophy and interstitial fibrosis.

The giant cell reaction around light chain casts was interpreted in the past as a syncytial cell formed from reactive or degenerating tubular epithelium.[5-7] Since the mid 1970's, however, this view has been

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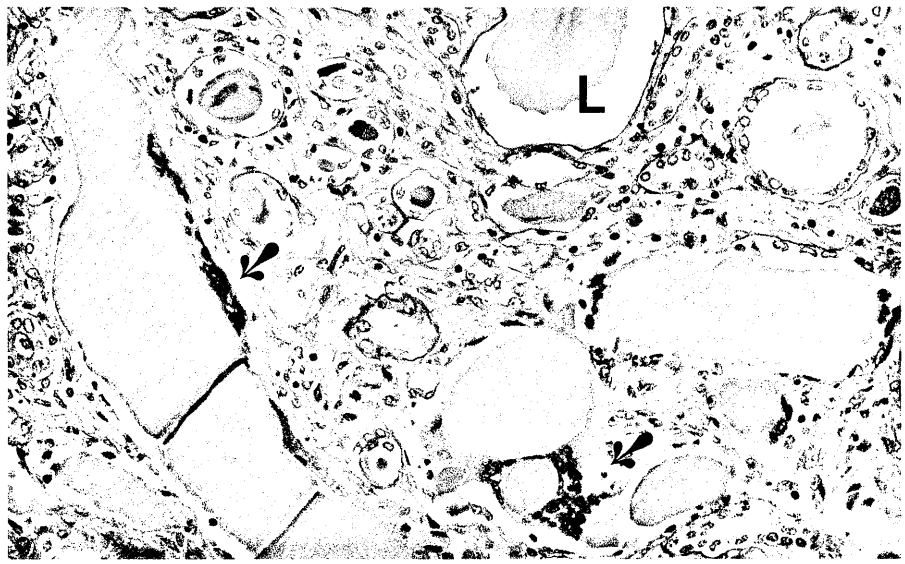

Fig. 1. Cast nephropathy. Autopsy material from a 67-year-old woman with multiple myeloma. Prominent large casts with numerous fracture lines, lamellation (*L*) and multinucleated giant cells (*arrows*) are noted. PAS, ×240

Table 1. Renal lesions of multiple myeloma and related disorders

I.	Cast nephropathy ("myeloma kidney")
II.	Fanconi syndrome
III.	Tissue deposition of monoclonal Ig-related material
	A. Non-organized (granular)
	Light chain deposition desease (LCDD)
	Light and heavy chain deposition desease (LHCDD)
	Heavy chain deposition desease (HCDD)
	B. Organized
	1. Fibrillar
	Amyloidosis
	AL amyloidosis
	AH amyloidosis
	Non-amyloid fibrillary glomerulonephritis (FG)
	2. Microtubular
	Immunotactoid glomerulopathy (ITG)
	Cryoglobulinemia
	3. Crystalline
IV.	Crow-Fukase syndrome
V.	Hypercalcemic nephropathy
VI.	Hyperviscosity syndrome
VII.	Hyperuricemic nephropathy
VIII.	Pyelonephritis
IX.	Neoplastic cell infiltration

changed: based on light and electron microscopic study, these cells are now suggested to originate from infiltrating monocytes.[4,8] Recent reports have confirmed this by using lectin and a well-characterized antibody against human macrophages.[9–11] The responsible cells appear to migrate through a ruptured tubular basement membrane.[4]

Immunofluorescent studies demonstrated that these casts usually contain various immunoglobulins and light chains, Tamm-Horsfall protein, albumin, and other proteins.[4,12] Although the light chain produced by the myeloma is predominant, cases with casts containing only one type of light chain are rare.[12] The casts may have a central, less intense staining zone and more heavily staining rim with all antisera.

Tamm-Horsfall protein is demonstrated in most casts. This protein is synthesized exclusively by cells of the thick ascending loop of Henle, and is ordinarily present only in the distal nephron—which is also the initial site of cast formation in the myeloma kidney. Its isoelectric point is very low.[13] It has been suggested that light chains with high isoelectric points are more nephrotoxic than those with low isoelectric points.[14,15] This concept appears to have certain validity for cast formation with Tamm-Horsfall protein. However, these observations have not been confirmed by others.[16,17]

In one-half of the cases of a study,[10] Tamm-Horsfall protein and other distal tubular markers were found in Bowman's space, being almost always associated

with interstitial deposits of Tamm-Horsfall protein; these markers were virtually never noted in Bowman's space of plasma cell dyscrasia patients without numerous large casts. This suggests that there are communications between distal and proximal nephron, most likely by an intraluminal reflux but possibly also through breaks in the tubules and via the interstitium. Thomas et al.[18,19] suggested that proteolytic enzymes and reactive oxygen metabolites released by the interaction between Tamm-Horsfall protein and neutrophils or mononuclear phagocytes through cell surface receptors might induce tissue damage. Recent work on growth factors in monoclonal-light-chain-related diseases suggested that the insulin-like growth factor and transforming growth factor-beta (TGF-β) staining in the tubular interstitium correlated to tubular damage, and that fibroblast growth factor correlated also to interstitial fibrosis.[20]

The casts have a pleomorphic appearance at the ultrastructural level. Some are extremely dense and homogenous, others less dense and finely granular, and a third type of variable density, but quite coarsely granular. In addition, cellular debris and fibrillar material, consistent with Tamm-Horsfall protein with a diameter of 4 nm, can be observed in some of the casts.[4] Degenerative changes such as vacuolation, loss of the brush border and desquamation of cell fragments of the tubular epithelial cell are nonspecific, but there is marked activation of the lysosomal system of the proximal tubules. Some lysosomes appear markedly enlarged, distorted and atypical in appearance.[21]

A myeloma cast has been found in the urine sediment of 20% of patients with multiple myeloma.[22] This cast is characterized by a granular to waxy matrix which appears glassy or laminated in texture, with syncytial arrangement of histiocytic giant cells attached or embedded in the cast.

Renal response to exposure to Bence Jones proteins (BJP) is apparently not uniform. Some patients may excrete large amounts of BJP for years and yet maintain normal renal function.[23,24] Koss et al.[25] reported that the intraperitoneal injection of a human BJP into mice resulted in cast nephropathy, but two other proteins failed to produce comparable changes. Solomon et al.[26] used the same animal model and assessed the nephrotoxic potential of a large number of well-characterized human BJP obtained from patients for whom the renal function and pathological data were available. They found that the kidney lesions produced by the injection of BJP tend to mimic those in the kidney of the patient from whom the protein was obtained. Thus, particular BJP are primarily responsible for producing the distinctive types of protein deposition in renal tissue and the clinical manifestations that occur in patients with light chain-associated disease.

A marked reduction or disappearance of light chain casts on repeated biopsy or autopsy was shown as a result of chemotherapy. However, in some cases the light chain casts were replaced by massive paraprotein deposits,[27] suggesting that chemotherapy had altered the structure of the light chains involved, as had been earlier documented clinically[28] and experimentally.[29]

Light chain cast nephropathy was found in cases with rifampin-associated renal failure. In contrast to myeloma kidney, in these cases heterogenous (both kappa and lambda) light chains are reported to be involved.[30,31] Excessive soluble proteins other than light chains, which are freely filtered by the glomerulus and are subsequently precipitated in the distal nephron, can cause myeloma-like cast nephropathy.[32,33]

The Fanconi syndrome

Tubular lesions associated with light chain proteinuria can be manifested as defects in proximal tubular function or distal nephron injury. The latter is associated with distinct morphologic pictures of light chain cast nephropathy. The former are responsible for a distinct clinical syndrome, the acquired Fanconi syndrome.

In a series of 37 patients with Bence Jones proteinuria, 22 had at least one tubular transport abnormality, and only three patients had four or more transport abnormalities, i.e. the classical Fanconi syndrome.[34] In two thirds of the cases, Fanconi syndrome preceded the development of overt myeloma, often for many years.[35]

Findings at renal biopsy were almost normal in some cases,[36] but several nonspecific changes—including the presence of cytoplasmic crystals of proximal tubular cells—were reported.[37,38] An improvement in the tubular functions with the disappearance of the BJP was noted after treatment for myeloma,[39] which suggests a pathogenetic role for monoclonal light chains.

Intracellular protein crystals are found in some cases in plasma cells and renal tubular cells,[35,37,38] but are not as specific for Fanconi syndrome as previously thought.[40] Aucouturier et al.[41] suggested that the proclivity of monoclonal light chains to autoaggregation and their ability to generate a proteinase-resistant fragment might lead to crystallization and renal impairment. Fanconi syndrome light chains, in contrast to those of cast nephropathy, were reported

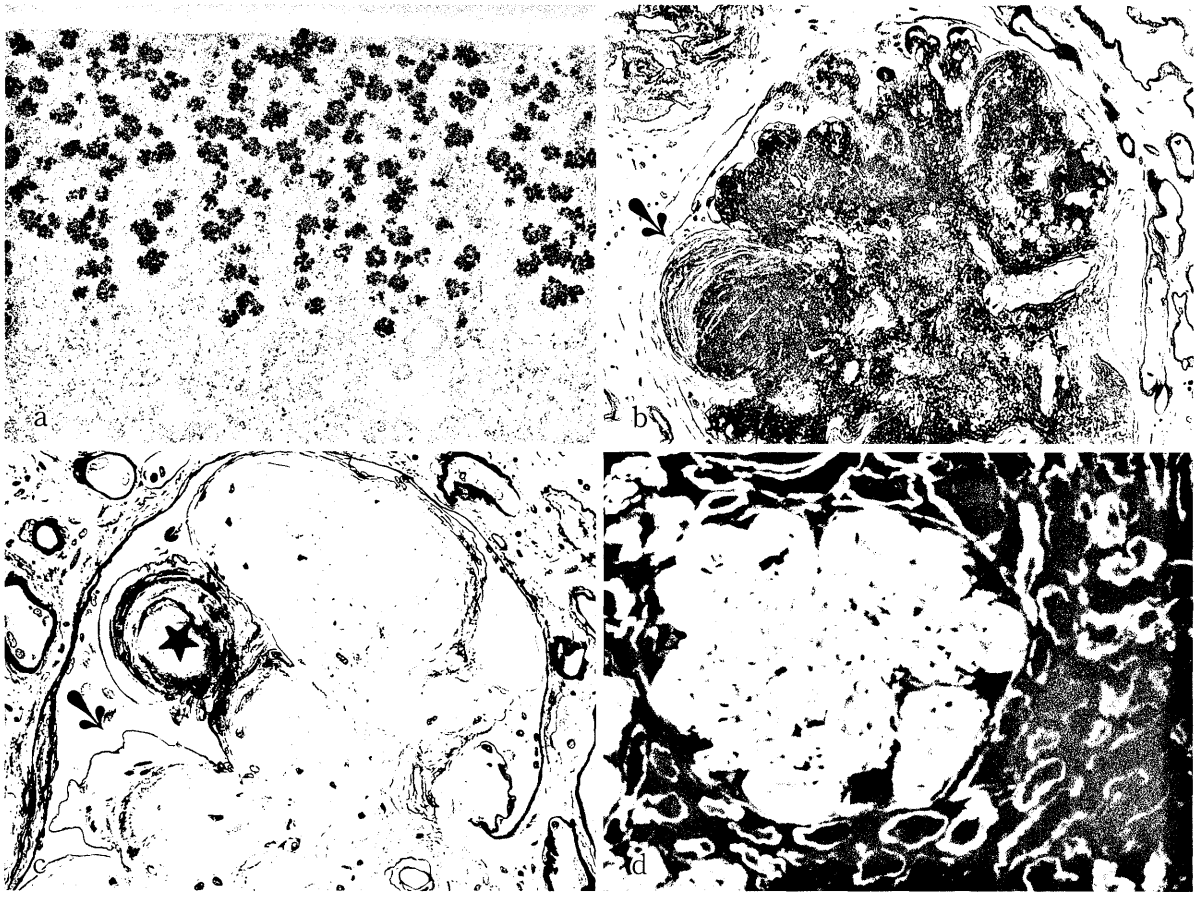

Fig. 2. LHCDD. Autopsy material from a 60-year-old man with IgD-λ myeloma. **a.** Low power view of the histologic section showing enlarged glomeruli, which are visible even to the naked eye, with a deposition of strongly PAS positive material. PAS, ×9 **b.** One nodule (*arrow*) opposite the vascular pole is peripherally lamellar and less strongly stained with PAS. PAS, ×160. **c.** One nodule (*asterisk*) is peripherally lamellar and overlaid with a dilated capillary lumen, while another nodule (*arrow*) has the same appearance but to a lesser degree. The deposited material is non-argyrophilic. PASM, ×250 **d.** A delta heavy chain is present in the glomerular nodular lesions and basement membranes of glomerular capillaries, Bowman's capsule and tubules. A lambda light chain is also present in the same fashion. Fluorescein-labelled anti-δ antiserum, ×100

to show no reaction with Tamm-Horsfall protein.[42]

Non-organized immunoglobulin deposition disease

In 1976 Randall et al.[43] recognized the systemic nature of light chain deposition disease (LCDD), which prominently involves the kidney. Soon after this first description, monoclonal heavy chains were found together with light chains in the tissue deposits from certain patients (light and heavy chain deposition disease, LHCDD).[28] More recently, patients with deposits containing monoclonal heavy chains without the co-deposition of light chains (heavy chain deposition disease, HCDD) have been reported.[44–46] Since these three diseases are essentially similar in clinical and pathological terms, the more inclusive term "non-amyloid immunoglobulin deposition disease,"[47,48] or "monoclonal immunoglobulin deposition disease,"[49,50] has been proposed. Still, non-amyloid immunoglobulin deposition disease has been used as a proper name for these three deposition diseases from the morphological point of view, since morphologically distinct amyloidosis and immunotactoid nephropathy are included in monoclonal immunoglobulin deposition disease of a wider sense.[51] For the same reason, non-organized (or granular) immunoglobulin deposition disease (NOIDD) or Randall type may be a more precise name to distinguish this from non-amyloid

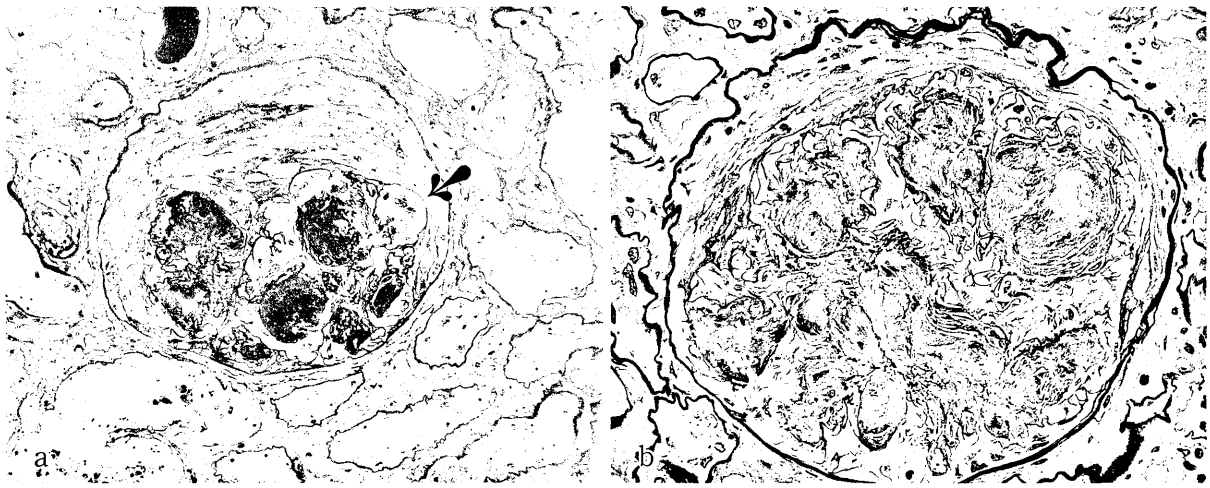

Fig. 3. LHCDD. Biopsy **a** and autopsy (**b**, three months later) materials from a 70-year-old woman with IgG-λ myeloma. **a.** A glomerulus with nodular lesions and crescent formation, and a multinucleated giant cell is found intracapillarily. (*arrow*) Azan, ×175 **b.** A representative glomerulus with lamellar nodules, which are supposed to be related to mesangiolysis, and fibrous crescent. PAS, ×250

fibrillary glomerulonephritis.

The majority of the patients exhibit glomerular symptoms, and abundant albuminuria often leads to a full-blown nephrotic syndrome. In some cases the renal function deteriorates rapidly with the features of rapidly progressive glomerulonephritis.[2,52,53]

On immunofluorescence, the pathognomonic finding in NOIDD is the diffuse linear staining of the basement membrane of tubules, Bowman's capsule and glomerular capillaries for a single light chain (LCDD), light and heavy chains (LHCDD) (Fig. 2c), or heavy chain (HCDD).

The glomerular appearance most commonly found in light microscopy is that of nodular glomerulosclerosis. These nodules give negative reactions for amyloid stains and are intensely eosinophilic and periodic acid-Schiff (PAS) positive. The distribution of the nodules is fairly regular (Fig. 2a). The glomerular basement membranes typically appear slightly rigid and show a mild thickening. In advanced cases the loops are nearly obliterated by the nodules.

Although the nodular lesions in NOIDD may be similar to those found in diabetic glomerulosclerosis, in diabetic nephropathy the glomerular basement membranes are markedly thickened. Other diabetic lesions such as capsular drops, exudative fibrin-caps, and extensive hyalinosis of the efferent arteriole are not observed in NOIDD. By periodic acid silver methenamin stain (PASM), in contrast to argyrophilic diabetic nodules, most of the glomerular nodules in NOIDD are nonargyrophilic (Fig. 2b), apparently due to the replacement of the mesangial matrix by deposited protein, though some nodules show an argyrophilic lamellar appearance with an overlaid aneurysmal cystic lesion (Figs. 2b, 3b). The latter appear to be related to mesangiolysis,[48,54] and the morphogenesis is similar to classical Kimmelstiel-Wilson nodules.[2,55]

The differentiation from amyloidosis is made by Congo red negativity, but the combination of NOIDD nephropathy and amyloidosis has been reported.[56–59]

Although paraprotein deposition is listed as one of the fundamental processes which result in a membranoproliferative pattern glomerular injury,[60] in primary membranoproliferative or lobular glomerulonephritis, mesangial cell proliferation and an increase in the argyrophilic mesangial matrix are much more prominent. However, in occasional cases of NOIDD, there is prominent endocapillary proliferation, and in a few, conspicuous crescent formation is also observed[53] (Fig. 3a). Capillary aneurysms tend to be prominent in cases with severe proliferative changes and crescents.[2,61]

The typical nodular lesions are not as frequent as previously thought. Their actual incidence is about 30–50% of cases.[62] Most other patients have mild glomerular lesions with a thickening of the glomerular capillary walls with or without moderate enlargement of the mesangium. Light microscopically, about 10% of patients have nearly normal glomeruli (Fig. 4). Herrera et al.[20] reported that cases with mesangial expansion showed an impressive staining of TGF-β in glomeruli, while a case without mesangial nodules did not. Another investigation using a

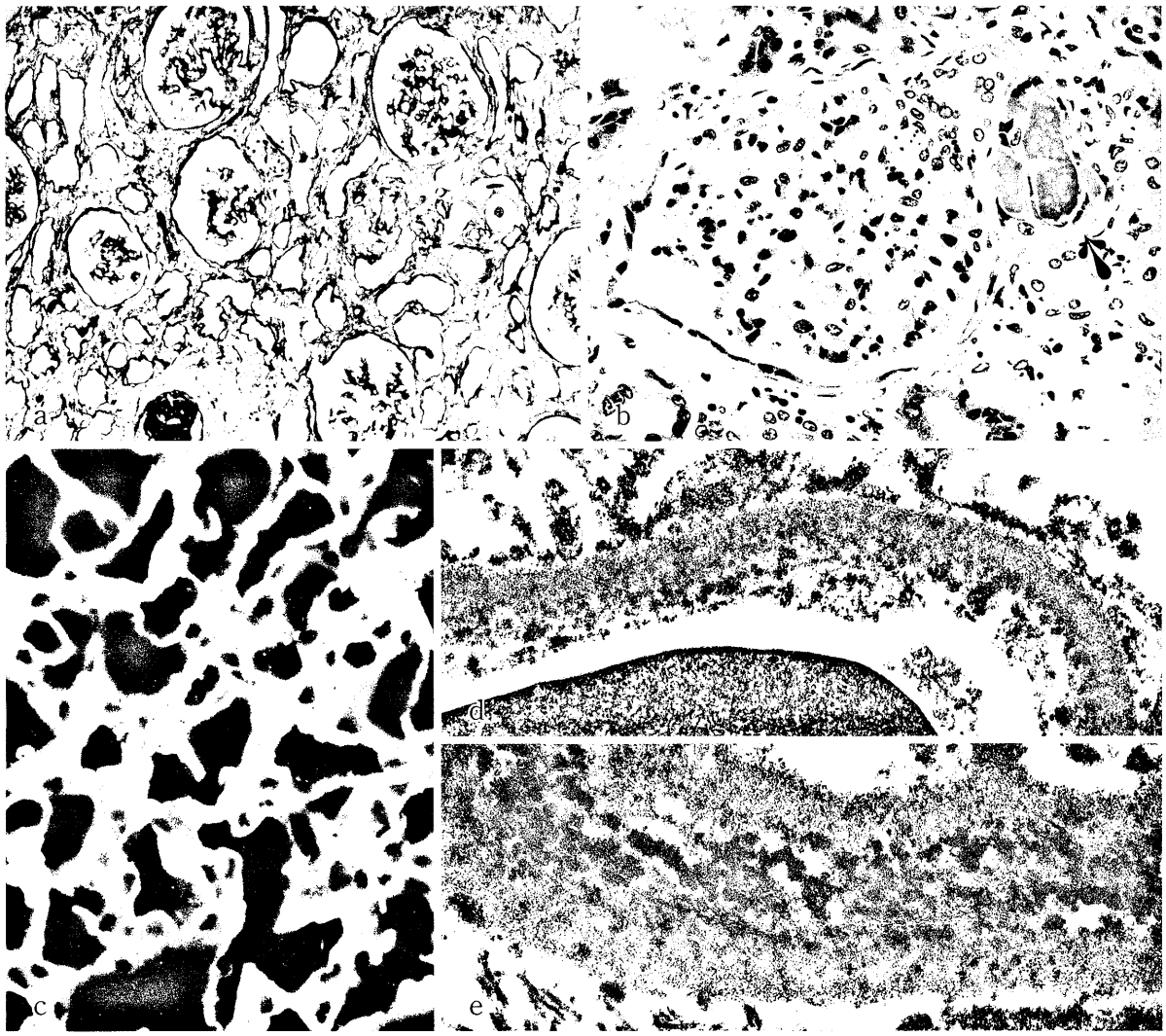

Fig. 4. LCDD. Autopsy material from a 69-year-old woman with chronic renal failure of clinically undefined etiology. M protein (−). **a.** Marked atrophic tubules and almost normal appearing glomeruli are found. PASM, ×120 Routine immunofluorescence study using anti-heavy chains and anti-complement sera revealed no specific deposition in the glomeruli. **b.** A few casts with giant cell reaction (*arrow*) are found. HE, ×270 In the bone marrow small clusters of atypical plasma cell are found. **c.** Kappa chain, but no lambda chain, is linearly deposited in the basement membranes of liver sinusoid (Fluorescein-labelled anti-λ antiserum. ×320 By electron microscopy granular deposits are found in the glomerular basement membrane **d** and tubular basement membrane, **e**. ×25,700

cell culture model by the same group[63] demonstrated that light chains from the urine of patients who had biopsy-proven nodular glomerulosclerosis associated with light chain deposition disease inhibited mesangial cell proliferation and increased the production of mesangial matrix proteins. Additionally, immunocytochemistry and bioassay proved TGF-β production and activity to be increased when mesangial cells were exposed to these proteins. These findings were not observed in mesangial cells exposed to human albumin and other light chains previously characterized as tubulopathic. They concluded that increased TGF-β activity by certain light chains appeared to be a key pathological mechanism of the disease.

The tubular basement membranes are usually thickened and appear eosinophilic, PAS positive and ribbon-like. The thickening is most prominent in the medulla. However, the degree of thickening varies by case due to the marked variation in the amount and extent of deposits. The tubular epithelium is often

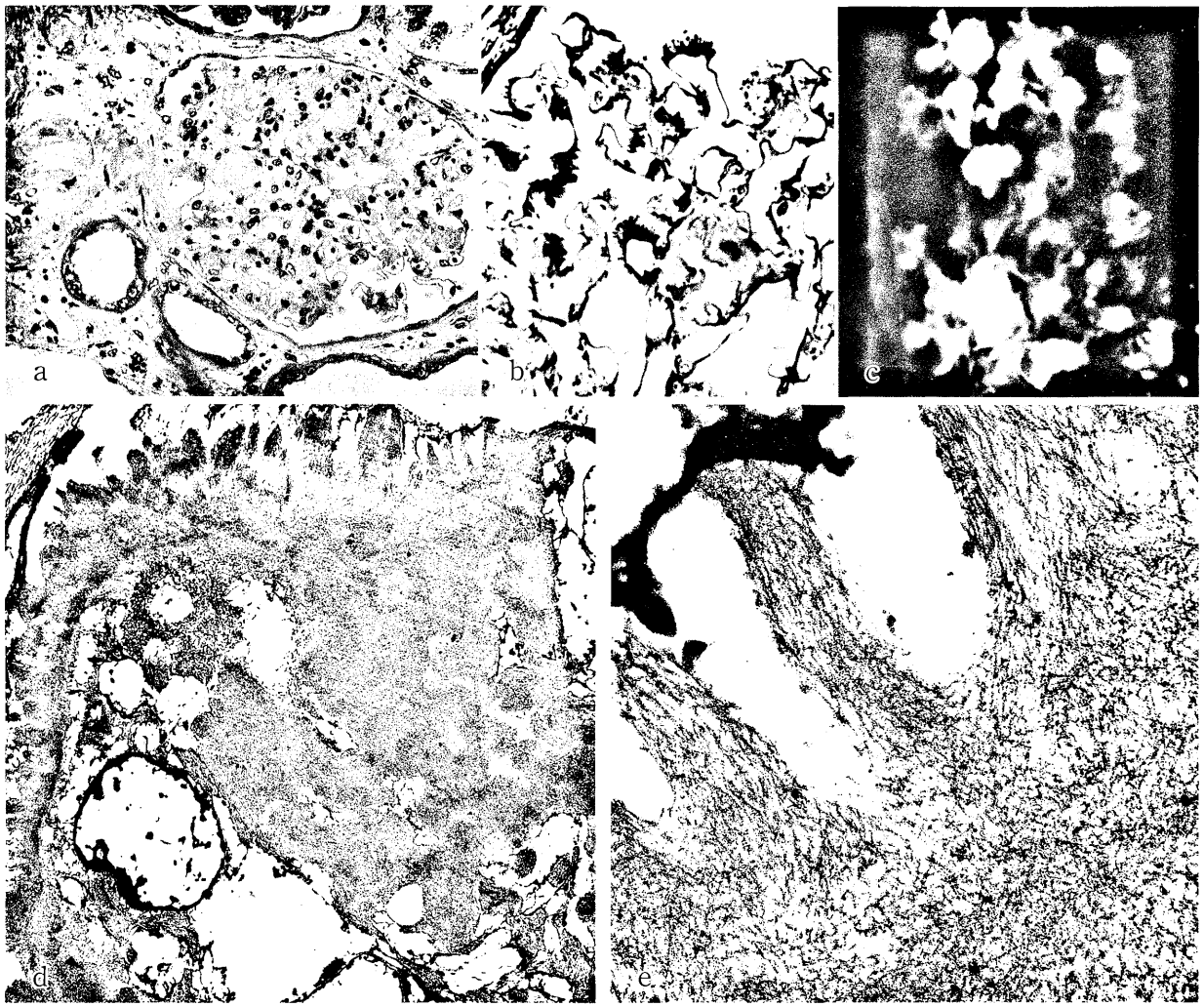

Fig. 5. AL amyloidosis. Autopsy material from a 59-year-old woman with IgA-λ myeloma. **a.** Eosinophilic amorphous material is found in the arteriole and mesangial areas of the glomerulus HE, ×160. **b.** By PASM, staining, spicules are conspicuous along the outer aspect of the capillary walls of the amyloid deposited area. PASM, ×410 **c.** Amyloid deposits are confluent and irregularly distributed in the glomerular tufts (Fluorescein-labelled anti-λ antiserum. ×320 **d.** Amyloid deposits are found from the mesangial to the subepithelial areas. ×3,600. **e.** Spicular arrangement of amyloid fibrils on the outer aspect of the glomerular basement membrane. ×38,000 **Figs. 5e, 6d** and **7d** are at the same magnification for comparison.

flattened and atrophic. A few characteristic myeloma casts surrounded by multinucleated giant cells are also found (Fig. 4b), but cast nephropathy and light chain deposition tend to occur in mutually exclusive fashion.[27]

Electron microscopically, fine granular electron dense deposits are found in the lamina rara interna of the glomerular basement membranes, and in the outer aspect of the tubular basement membranes. The deposits in the tubular basement membranes are more constant and heavy (Fig. 4d, e). When deposits in the mesangium are massive, they appear amorphous under low magnification but still fine granular at high magnification.[48] In cases with conspicuous crescent formation, ruptures of the glomerular basement membrane are found.[2]

Amyloidosis

Amyloidosis related to immunoglobulin should be included in organized immunoglobulin deposition disease (Table 1), but in this paper it is described separately for historical considerations and convenience.

Amyloid is defined by its tinctorial properties with the dye, Cong red, and by its ultrastructural morphology. AL amyloid, derived from the immunoglobulin light chains (or fragments there of), was the first type of amyloid to be successfully characterized biochemically, in 1971.[64,65] Since then, about twenty biochemically distinct precursor proteins of amyloid have been described.[66]

Amyloidosis is observed only in 7 to 11% of patients with myeloma.[67,68] Even in light chain myeloma, amyloidosis developed in 20%, while Bence Jones proteinuria is detected in 80%.[69] This low incidence may be explained by the fact that a biopsy for amyloid is not generally done,[67] but may indicate that only certain BJP are amyloidogenic.

Renal involvement in amyloidosis is common and the kidney is affected early in the disease. Furthermore, renal amyloidosis is an important cause of death in systemic amyloidosis of any type.

Amyloid is a weakly eosinophilic, noncellular material which looks homogenous light microscopically (Fig. 5a). It stains orange with Congo red and displays apple-green birefringence under polarized light. Amyloid desposits may involve all components of the kidney, but they usually predominate within the glomeruli, where both mesangial and basement membrane deposition occurs. Spicularly arranged amyloid deposits in the glomerular capillary walls[70,71] (Fig. 5b) are found more frequently and extensively in AL amyloidosis than in AA amyloidosis, so-called secondary amyloidosis associated with chronic active diseases, and are most closely associated with proteinuria.[72,73]

The pattern of immunofluorescence staining is confluent, nongranular, nonlinear and irregularly distributed—most prominently in the mesangium —with irregular ribbon-like extensions along the capillary wall (Fig. 5c). Variable staining of the tubular basement membranes and vessels was also reported.[74]

The AL deposits can be of either light chain type, but are more frequently derived from λ light chain.[75] However, there are reports that in AL amyloid the deposits are stainable with standard antisera to κ or λ in only about one-half of all cases, probably because the light chain fragment in the fibrils is usually the N-terminal variable domain, which is largely unique for each monoclonal protein.[76]

Like other types of amyloid, AL amyloid contains the amyloid P component. The amyloid P component and apolipoprotein E were detected in the light chain amyloid but not in nonorganized monoclonal light chain deposits, and were suggested to be related to fibrillogenesis.[77]

Electron microscopically, the amyloid fibrils are present in random arrays of regular nonbranched fibrils measuring approximately 8 to 12 nm in width (Fig. 5e). However, in the subepithelial regions, nearly parallel arrays which give rise to the spike-like projections noted by light microscopy are observed (Fig. 5d). Segmental loss or breaks in the basement membrane which are replaced by amyloid fibrils are frequently observed.[78]

Amyloid fibrils cannot always be convincingly identified ultrastructurally, and electron microscopy alone is not sufficient to confirm the diagnosis of amyloidosis.[66] At one time, the ultrastructural examination of urinary sediments was considered to be a useful method for diagnosis of amyloidosis,[79,80] but patients with amyloidosis have had negative results, and amyloid-like fibrils have been found in the urine of patients without amyloidosis.[81–83] Consequently, the examination of urinary sediments is actually not helpful.

The inherent amyloidogenecity of particular monoclonal light chains has been confirmed in an *in vivo* model in which isolated BJP are injected into mice. Animals receiving light chains from AL amyloid patients developed typical amyloid deposits composed of the human protein and mouse amyloid P component, whereas animals receiving light chains from myeloma patients without amyloid did not.[84]

The preferential association of light chains of the $V_{\lambda VI}$ subgroup with AL amyloidosis was reported,[85] but no common primary structural features have been identified that distinguish an amyloid from a non-amyloid light chain.[86] A recent paper reported that human κ_{IV} light chain variable domains could be produced by recombinant methods in E. coli.[87] The ability to generate and modify human light chains by recombinant means will provide a system for identifying structural and chemical features of light chains that lead to amyloid formation.

Immunoglobulin heavy chains and their fragments have generally been deemed to the lack structures required for amyloid fibril formation, although once amyloid-like fibrils were produced *in vitro* from a heavy chain disease protein.[88] However, heavy chain-derived amyloidosis have recently been confirmed.[89–91]

Clinical remission and the gradual decrease of amyloid deposits, shown by scintigraphy, after syngeneic bone marrow transplantation in a patient with AL amyloidosis, have been reported.[92] Resorption of AL amyloid deposits with 4′-iodo-4′-deoxydoxorubicin has also been reported.[93] This compound was demonstrated to bind all five types of natural amyloid fibrils tested: immunoglobulin light chains, amyloid A, transthyretin, β-protein, and β2-microglobulin. It

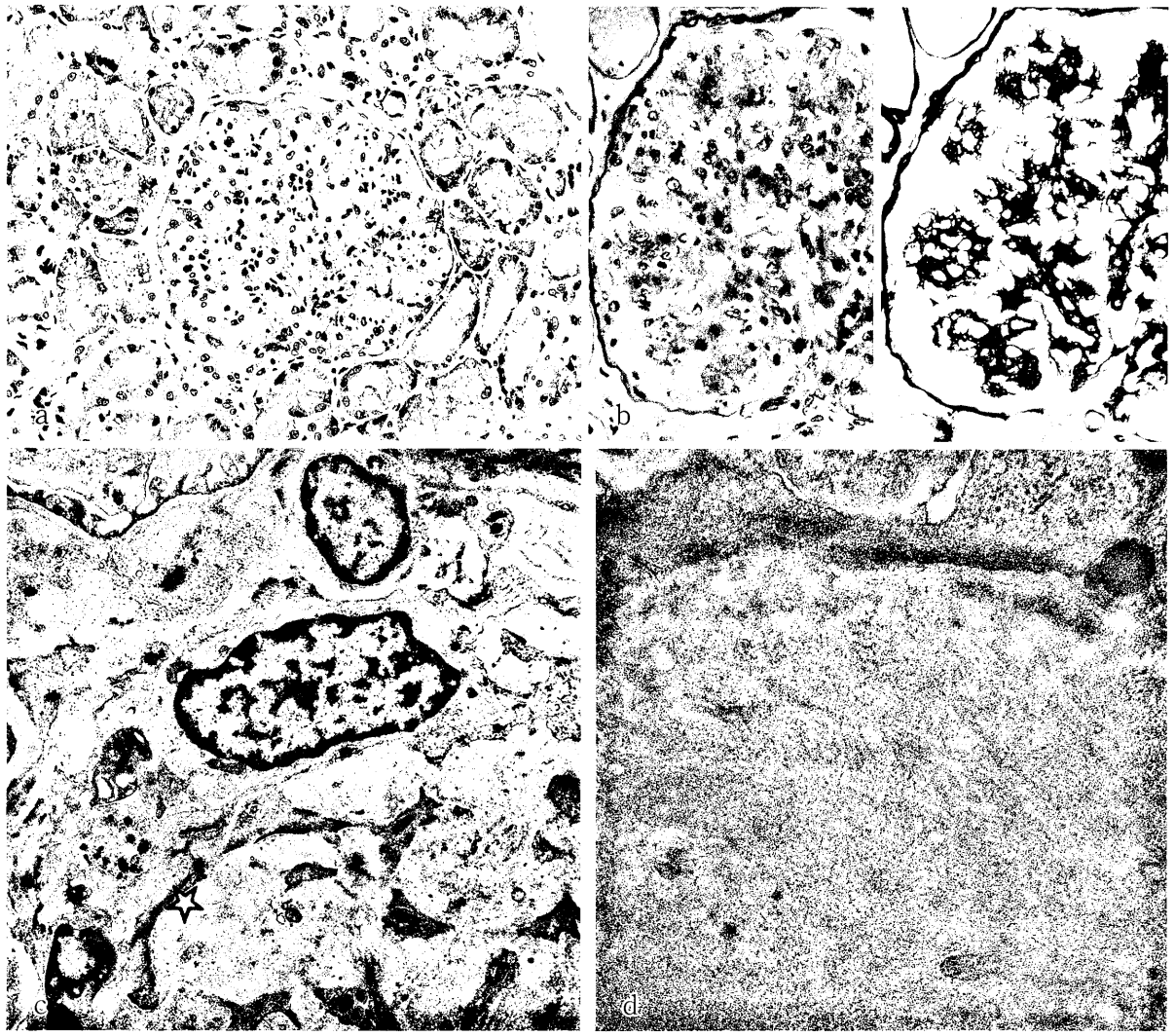

Fig. 6. Fibrillary glomerulonephritis. Biopsy material from a 59-year-old man with nephrotic syndrome (kindly provided by Drs. S. Nishi and M. Ueno, Second Department of Internal Medicine, Niigata University School of Medicine). **a.** Prominent glomerular findings are an expansion of mesangial areas and mild hypercellularity. HE, ×170 **b.** Expanded mesangial areas are PAS positive and argyrophilic. left PAS, right PASM, ×280 **c.** A marked increase of mesangial matrix is observed. ×2,700 **d.** At higher magnification, the mesangial matrix (*asterisked portion in* **c**) is filled with fibrillary material. ×38,000

further significantly reduced the formation of amyloid deposits in *in vivo* studies using an experimental amyloid murine model.[94] The therapeutic potential of this new drug in all types of amyloidosis is anticipated.

Organized immunoglobulin deposition disease

In 1977, Rosenmann and Eliakim[95] reported a case of nephrotic syndrome and fibrillary deposition in the glomeruli which appeared similar to an amyloid except for a larger fibril width and negative staining with Congo red. This was the first reported case of "fibrillary glomerulonephritis" or "Congo-red negative amyloid-like glomerulopathy." Similar glomerular fibrillar deposits in a patient with monoclonal IgG kappa gamma-globulinemia were also described in the same year.[96]

On the other hand, in 1980 the term "immunotactoid" was proposed to stress the organized orientation of deposits and their immunoglobulin deposition for organized microtubular deposits in a patient with nephrotic syndrome.[97] The deposits contained IgG_3 with a κ-chain and were postulated to be related

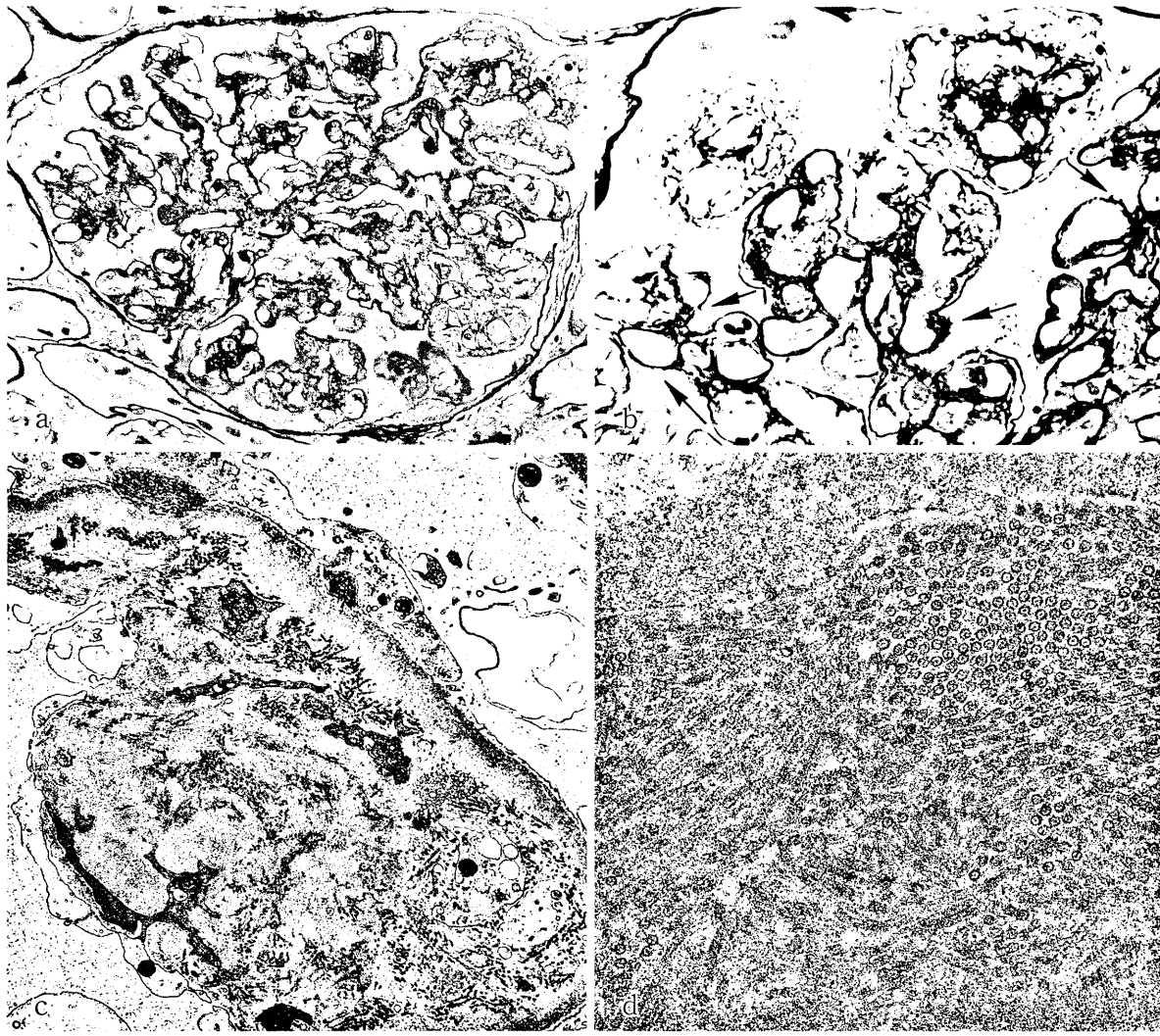

Fig. 7. Immunotactoid glomerulopathy. Biopsy material from a 72-year-old man with nephrotic syndrome. M protein (−), cryoglobulinemia (−). **a.** In addition to a mild, diffuse increase in the mesangial cell and matrix, marked segmental proliferative changes with double contour of the capillary wall are observed. PAS, ×300 **b.** PASM, staining reveals a few spikes (*arrows*) on the epithelial aspect of the glomerular basement membrane. PASM, ×560 **c.** Organized dense deposits are seen in the mesangium and subepithelial space. ×8,000 **d.** At higher magnification microtubular structures are recognizable. On cross section the cylindrical profiles have a electron dense core. ×38,000 In this patient, the only evidence indicating the association of monoclonal immunoglobulin is that the deposited light chain in the glomeruli is exclusively kappa chain.

to paraproteinemia, in spite of normal bone marrow morphology, normal serum protein electrophoresis and quantative immunoglobulin, and the absence of Bence-Jones proteinuria. Subsequently, some authors have used the term "immunotactoid glomerulopathy" to encompass both cases with fibrillary deposits and microtubular deposits.[98-100] However, recent studies have proposed a distinction of cases with deposits characterized by smaller, randomly arranged fibrils from those with deposits exhibiting microtubular features or crystalline arrays.[101-104]

From the published data, the incidence of an overt or latent immunoproliferative disorder appears to be high when immunoglobulin deposits show a microtubular organization, but low in fibrillar immunoglobulin deposits. At any rate most, if not all, incidences of immunotactoid glomerulopathy and some of fibrillary glomerulonephritis are related to monoclonal immunoglobulinemia.

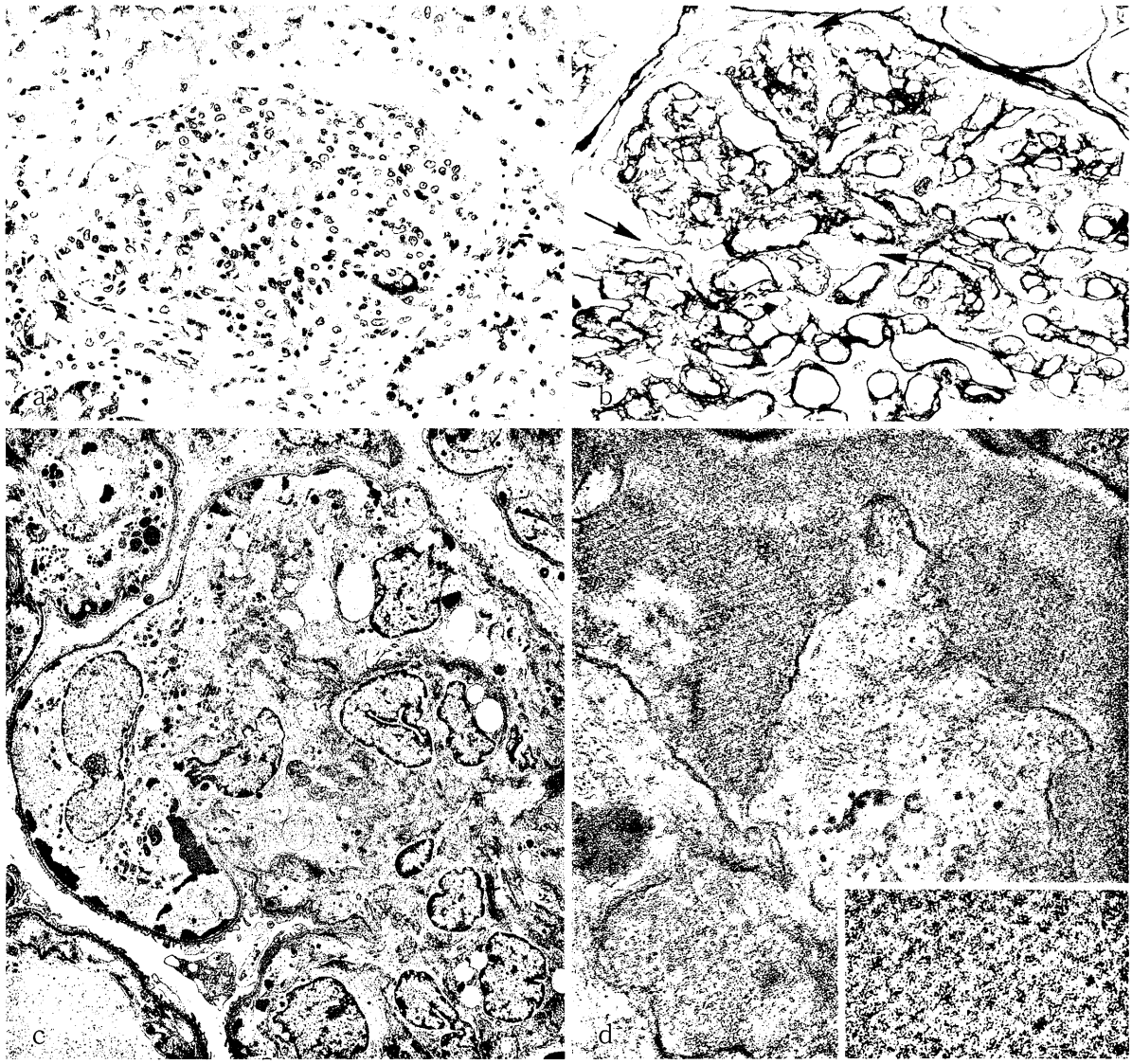

Fig. 8. Crystalline deposition disease. Biopsy material from a 36-year-old man with nephrotic syndrome. IgG-λ M protein (+), cryoglobulinemia (−). **a.** Prominent expansion of mesangium with hypercellularity is noted. HE, ×175 **b.** PAS staining reveals extensive double contours of the capillary walls and large deposits (*arrows*) located in subendothelial and mesangial areas. PAS, ×350 **c.** Mesangial interposition is extensive. Infiltrating cells are noted in addition to increased mesangial cells. Large electron dense deposits are mainly located on the inner aspect of the basement membrane. ×2,150 **d.** At higher magnification deposits are composed of crystals, showing parallel lines or a lattice network (**inset**), depending upon the phase of sectioning. ×5,300 *inset*, ×96,000

Fibrillary glomerulonephritis: In 1983 Duffy et al.[105] reported eight patients containing abundant fibrils in their mesangial matrix and basement membranes, and suggested that such non-amyloid fibrils were generally larger. They proposed the name "glomerulonephritis with fibrillary deposits," which was later modified to "fibrillary glomerulonephritis"[106] or "fibrillary glomerulopathy."[107]

The light microscopic expression of fibrillary glomerulonephritis varies. The most common abnormalities are capillary wall thickening and mesangial expansion either with or without cell proliferation (Fig. 6a, b). Other appearances of reported cases are membranous glomerulonephritis, proliferative glomerulonephritis, membranoproliferative glomerulonephritis, or amyloidosis. Glomerular microaneurysms

are also reported.[108]

In immunofluorescence study, glomeruli almost invariably show a strong staining for IgG and C_3, though less frequently for IgM. The staining is diffuse and global. The immunoglobulins are polyclonal, but 10 to 20% of the cases show monoclonal, usually IgG-κ. In a small percentage of cases, fibrillar deposits do not stain for immunoglobulins.[109]

By electron microscopy, the deposits consist of randomly oriented, nonbranching fine fibrils similar to amyloid fibrils, although generally thicker, the most common diameter being around 20 nm (Fig. 6c, d).

Immunoelectron microscopy reveals that the immunoglobulin, complement and amyloid P component are in the fibrils.[110] This suggests that the fibrils are composed of either immune complexes or aggregated immunoglobulin that is capable of an activating complement. It was reported that aggregated human myeloma proteins could activate the complement by an alternative pathway.[111] The amyloid P component is detected in fibrillary glomerulonephritis, but not in granular deposits of LCDD, indicating a relationship between amyloid P component and fibrillogenesis.[112] A few authors have described the presence of fibrils within the mesangial deposits of LCDD.[113,114]

Extrarenal deposits of a fibrillar material,[115,116] and the recurrence of fibrillary glomerulonephritis in renal allograft[106] suggest that some patients with this disease may have a circulating factor responsible for the deposition of fibrillary material.

As the number of reported cases increases, it has become clear that only a minority of patients show oligoclonal or monoclonal immunoglobulin deposition. At present, fibrillary glomerulonephritis is apparently formed of several heterogenous diseases. Actually a new entity, "familial glomerulopathy with massive deposits of fibronectin", fomerly included in fibrillary glomerulonephritis, was recently proposed.[117–119]

Fibrils of fibrillary glomerulonephritis must be differentiated from other fibrillar structures observed within glomeruli by electron microscopy. A small, scattered accumulation of 5 to 20 nm fibrils are occasionally seen in a variety of sclerosing glomerular diseases, such as diabetic glomerulosclerosis,[120,121] focal segmental glomerulosclerosis,[122] and transplant glomerulopathy.[123] These fibrils do not correspond to immune deposits and are probably derived from the thinner filaments which make a network in the normal mesangial matrix and basal lamina.[124]

Collagen fibers are not difficult to distinguish from fibrils of fibrillary glomerulonephritis. They are thicker (30–120 nm) and show distinct periodicity. The best known disease in which periodic collagen fibers are found within glomeruli, mainly in the basement membrane but scarcely in the mesangium, is nail-patella syndrome.[125] Recently, a new entity has been reported mostly from Japan and called collagenofibrotic glomerulopathy; it is characterized by the massive glomerular deposition of periodic collagen fibers, especially in the mesangium and subendothelial zones.[126]

Immunotactoid glomerulopathy: Glomerular lesions of immunotactoid glomerulopathy resemble those of membranoproliferative glomerulonephritis. Membranous transformation is also associated (Fig. 7a, b), and sometimes referred as atypical membranous glomerulonephritis.[127] Stains for amyloid are negative. Leukocytoclastic vasculitis in the skin—similar to that in cryoglobulinemia—was reported.[128,129]

In immunofluorescent study, IgG and C_3, and occasionally IgM or IgA, are demonstrated. In some cases only one light chain (usually kappa) is found.

The glomerular deposits show a microtubular organization by electron microscopy, with parallel microtubules forming bundles oriented in all directions. The diameter of the microtubules ranges from 20–50 nm. Deposits are located in the mesangium and glomerular capillary wall (Fig. 7c, d).

Crystalline deposition disease: Widespread crystalline deposits of paraprotein in many organs have been reported.[130–132] In the kidney, crystalline deposits are usually prominent in tubular epithelial cells, but deposits in glomeruli are also reported.[132,133] In most of these cases, crystalline deposits are found as rhomboid, diamond- or neddle-shaped intracytoplasmic inclusions, and some ultrastructurally reveal a lattice network appearance[134] which resembles that found in crystalline inclusions of myeloma cells.[135] Extracellular crystalline deposits in glomeruli revealing a lattice network[136] (Fig. 8) or microlamellar structures[137] have also been reported.

Extensive crystalline deposition in vascular and extravascular spaces may mimic clinical symptoms of systemic necrotizing vasculitis.[138]

Waldenström's macroglobulinemia

Waldenström's macroglobulinemia (WM) is classified as a plasma cell dyscrasia associated with IgM monoclonal gammopathy. Generalized lymphadenopathy and hepatosplenomegaly are frequent findings.

Multiple myeloma of IgM type is rare and has been confused with WM; its existence has not been accepted in general.[139] However, there were reports of IgM myeloma as a distinct entity,[140,141] but clinical

manifestations, such as retinal hemorrhage and neurological signs and symptoms, are understood to be common to those of WM, resulting from an abnormal increase in serum IgM.[141]

Renal involvement in WM is variable, including glomerular IgM thrombi, amyloidosis, cryoglobulinemic glomerulonephritis, neoplastic lymphocytic infiltration of the kidney and cast nephropathy. The characteristic glomerular lesion of WM is the presence of amorphous deposits in the capillary lumens, often called thrombi.[142] They are strongly PAS positive. Glomerular lesions of a mesangiocapillary type[143] and crescentic glomerulonephritis[144] were also reported.

In immunofluorescence study, the thrombi stain only for IgM and for the light chain corresponding to the serum M protein.

Electronmicroscopically, a fibrillar-crystalline substructure of deposits has been reported.[145]

Amyloidosis develops in less than 5%,[146,147] and cryoglobulinemia is detected in approximately 15% of patients with WM.[148] Nephrotic syndrome is rare in WM, but when present it is usually caused by amyloidosis. However, some cases of nonamyloid nephrotic syndrome have been reported.[149,150]

Antibody activities of monoclonal immunoglobulins directed against autoantigens are sometimes found in patients with WM and other neoplasms of the immunoglobulin-producing cells.[151] Anti-IgG activity (rheumatoid factor) is a well known example, and cold agglutinin,[152] antibodies against myelin-associated glycoprotein,[153] cytoskeleton proteins,[154] and other substances[155] are known. The IgM antiglomerular antibody[156] and cold agglutinin[157] were found in patients with nephrotic syndrome, though their pathogenetic role was obscure. Autoantibodies against various nuclear antigens[158,159] and neutrophil cytoplasm[160] have also been demonstrated in patients with monoclonal gammopathies, although these rarely lead to a systemic disease. However, a case of LCDD with anti-neutrophil cytoplasmic antibody-associated vasculitis has been reported.[161]

Cryoglobulinemia

Cryoglobulins are circulating immunoglobulins that possess the physical properties of precipitation when cooled and of resolubilization when rewarmed. By immunochemical analysis, three types of cryoglobulin have been defined by Brouet et al:[162] Type I, a single monoclonal immunoglobulin which may be found in patients with multiple myeloma, WM, or monoclonal gammopathy of undetermined significance; Type II, a mixed cryoglobulin, usually a IgMκ with rheumatoid factor actively against polyclonal IgG, which has been thought to be found in patients without any apparent underlying disease, and termed essential mixed cryoglobulinemia; Type III, a mixed cryoglobulin, consisting of two polyclonal immunoglobulins, which is found in patients with autoimmune disorders, chronic infections, or chronic inflammatory conditions.

However, the recent high prevalence of hepatitis C virus infection among patients with essential mixed cryoglobulinemia,[163,164] and the concentrated viral RNA in the cryoprecipitate[164] have been confirmed. Schifferli et al.[165] found a high percentage of intermediary Types II-III cryoglobulins with oligoclonal IgM in hepatitis C-associated cryoglobulinemia and suggested that the natural history of the disease might start with polyclonal stimulation of B lymphocytes producing rheumatoid factors (Type III), followed by selection of a limited number of clones (Types II-III), leading to the expansion of a single clone (Type II, finally to Type I?). It has also been shown that hepatitis C virus is both a hepatotropic and lymphotropic virus,[166,167] and chronic hepatitis C virus infection is suggested to be responsible for the lymphoproliferative disorders, as Epstein-Barr virus can generate Burkitt's lymphoma.

Renal lesions associated with Type I monoclonal cryoglobulinemia are infrequent compared with the mixed cryoglobulinemia. Most cases show a diffuse endocapillary glomerulonephritis,[168-170] often a membranoproliferative type.[171-173] Many eosinophilic thrombi in the glomeruli were also reported in a patient with monoclonal IgMκ cryoglobulinemia, who developed fatal acute renal failure as a result of prolonged exposure in a cool room.[174]

Immunofluorescence studies reveal deposition of immunoglobulins, usually with C_3. Complement activation by a purified cryoglobulin alone has been described,[175] but in some cases circulating immune complexes (such as IgG-anti-IgG) may play a role in the pathogenesis of the glomerulonephritis.[172] In addition to the deposition in glomerular capillary walls, similar immunoglobulin deposition in visceral arteries and arterioles has been reported.[176]

By electron microscopy numerous electron dense deposits can be observed in the subendothelial space and mesangium. Although Bogaars et al.[177] observed a cryoprecipitable immunoglobulin in the serum of a patient with multiple myeloma, which showed a unique tubular crystal structures by electron microscopy, glomerular dense deposits vary by case, apparently depending on their biochemical composition, and are described as amorphous,[173] fibrillar,[171,172] microcrystalline,[172] or finger print.[170] However, serum

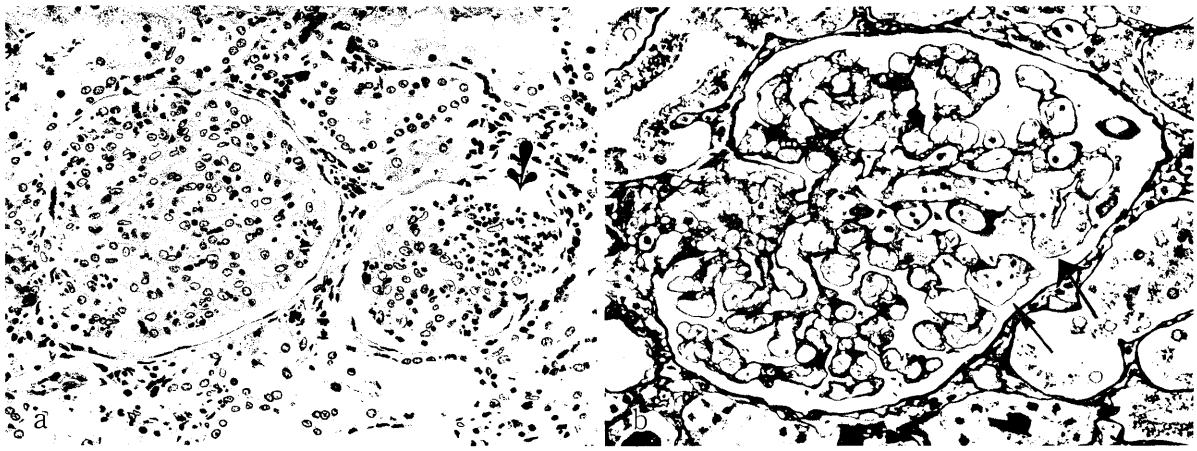

Fig. 9. Crow-Fukase syndrome. Autopsy material from a 38-year-old woman (kindly provided by Dr. K. Oyanagi, Brain Disease Research Center, Brain Research Institute, Niigata University). **a.** Glomeruli show diffuse moderate hypercellularity, and a rare aneurysmatic cystic lesion filled with red blood cells (*arrow*) is observed HE, ×175 **b.** By PASM staining mesangiolytic changes (*arrows*) are revealed in some glomeruli. PASM, ×285

cryoprecipitates are structurally similar to glomerular deposits in the same patient.[176]

The Crow-Fukase syndrome

Crow-Fukase syndrome,[178] also called Takatsuki's syndrome,[179] or POEMS syndrome[180] or Japanese multisystem syndrome,[181] is considered to be secondary to a plasma cell dyscrasia and characterized by the association of polyneuropathy, organomegaly, endocrinopathy, M-proteins and skin changes. The acronym POEMS derives from these five features.[180]

Cases with renal abnormalities are often reported by nephrologists, and reported incidences of azotemia and proteinuria in minor instances examined are 30% to 70%,[182–184] lower than those of multiple myeloma in general.[67] However, the renal impairment of this syndrome has not been emphasized, and many reviews did not mention it nor proteinuria,[178,185–187] although some early reports had described renal lesions.[188,189]

Renal glomerular lesions in this syndrome have been described as simulating membranoproliferative glomerulonephritis. Endocapillary proliferation, lobulation of the glomerular tuft and occasional double contours of the capillary walls present a resemblance to membranoproliferative glomerulonephritis (Fig. 9). However, opposed to idiopathic membranoproliferative glomerulonephritis, the glomerular immunofluorescence study has been negative or equivocal in a majority of cases examined.[179,183,185,189,190] More recently, the lucency of the widened subendothelial space[191]—the hallmark of microangiopathic nephropathy—and mesangiolytic lesions were added as characteristic findings[179,190] (Fig. 9b).

Surgical excision or irradiation of the local lesion and the administration of corticosteroids and/or anti-cancer drugs are reported to be effective in improving polyneuropathy and other systemic symptoms.[185] Such experiences suggest the existence of products from plasma cells, which are, however, likely to be different from immunoglobulins or light chains because of the negativity of the immunofluorescence study. Based on these findings it has been suggested that endothelial injury is an important mediator of the renal disease.[190] It has also been suggested that generalized endothelial injury may explain the multisystem manifestations. This hypothesis is supported by the findings of a concomitant microangiopathy in the vasa nervosum.[181,192,193] Endothelial cell injury in the liver with a deposition of amorphous material in the widened Disse's space was also reported.[194]

Castleman's disease, which has been reported to be due to an abnormal increase of interleukin 6 (IL-6) in the affected lymph nodes,[195] is often observed in Crow-Fukase syndrome.[178] Elevated serum IL-6 and the abnormal expression of IL-6 in the kidney in a case of this syndrome were reported.[196] IL-6 has also been identified as a major cytokine involved in the emergence of the tumor clone and tumor associated toxicities in patients with multiple myeloma.[197]

Hypercalcemia and other conditions

Hypercalcemia: Hypercalcemia associated with bony

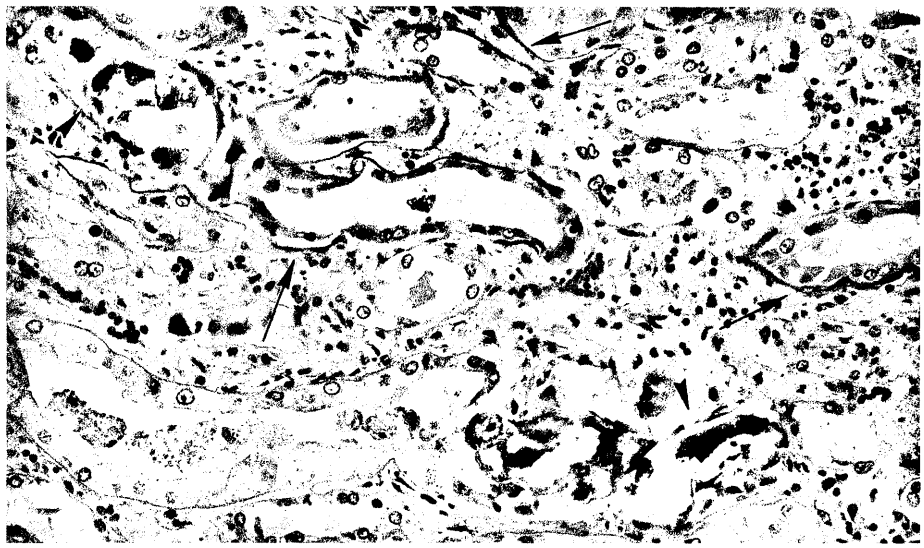

Fig. 10. Hypercalcemic nephropathy. Autopsy material from a 79-year-old man with IgG-λ myeloma. Hypercalcemia (+). Basement membranes of tubules (*arrows*) and intraluminal necrotic materials (*arrowheads*) are calcified. HE, ×240

complications may play a major role in renal insufficiency.[198] Histologic sections of bone are characterized by an increase in osteoclast activity occurring adjacent to the myeloma cells. Several osteoclast activating factors, such as lymphotoxins,[199] interleukin-1[200] and parathyroid hormone-related protein,[201] were reported to be produced by myeloma cells.

Hypercalcemia may induce vasoconstriction, volume depletion and renal tubular calcification. Even modest hypercalcemia administered together with BJP in the rat can result in a dramatic fall in the glomerular filtration rate, although virtually no adverse effect was obtained when either agent was given alone.[202] The findings suggest that the prediction of the nephrotoxicity of BJP may be rendered somewhat complex by the fact that other factors, such as hypercalcemia, may markedly alter the intrinsic properties of a given protein.

Tubular calcification may occur in multiple myeloma, though usually not extensively. Both proximal and distal tubules are involved, but in particular, basement membranes of the proximal segments become heavily calcified (Fig. 10). Calcification of glomerular basement membranes was rarely reported.[203] In addition, any degenerated or necrotic tissues tend to be infiltrated by calcium when the circulating calcium level is increased.

Renal dysfunction can also be induced by other pathologic factors associated with multiple myeloma, such as hyperviscosity of the blood, hyperuricemia and urinary tract infection (pyelonephritis), due to the propensity to infection.[204,205]

The hyperviscosity syndrome: The hyperviscosity syndrome as a common complication of patients with IgM paraproteinemia has been described clinically as the triad of bleeding, visual signs and symptoms, and neurological manifestations.[206] Symptoms usually occur when the monoclonal IgM concentration exceeds 3.0 g/dl, in contrast with the fact that monoclonal IgG or IgA levels of at least 5.0 g/dl are required.[207] Cases of the syndrome in association with light chain myeloma have also been reported.[208,209] The syndrome is sometimes associated with an impaired urinary concentration capacity disproportionate to the decrease in glomerular filtration rate.[210]

Hyperuricemic nephropathy: An elevated serum uric acid is a common biochemical feature in patients with multiple myeloma.[211] It is raised partly as a result of nuclear protein turnover associated with the increasing tumor mass, and partly as a consequence of dehydration and renal failure.

The precipitation of uric acid in the renal tubules and collecting system can lead to acute obstructive nephropathy and renal failure.[212] Even if hyperuricemia is not so marked, precautions should be taken against additional important factors including dehydration and acidosis, which favor uric acid crystal formation.

Neoplastic cell infiltration: In one report, 10% of autopsy cases had tumor infiltration in the kidney, though usually without clinical significance.[213] Plasmacytoma are rarely diagnosed in the kidney.[214,215] As extraosseous plasmacytomas of other organs they may be either isolated or accompany multiple myeloma.

The detection of myeloma cells in the urine sediment, which presumably indicates an extramedullary extension of myeloma, has occasionally been reported.[216,217]

The occurrence of multiple myeloma in patients with chronic renal failure is another issue. Non-Hodgkin lymphomas occur more commonly in organ-transplanted patients than in the general population.[218] They are usually of B-cell origin. The development of myeloma in renal transplant recipients is also well documented.[219,220] The increased incidence of malignancy during chronic renal failure without transplantation has also been reported,[221,222] and a few case reports on multiple myeloma occurring in chronic renal failure patients can be found.[223,224] Kinlen et al.[225] stated that the only type of malignant tumor for which there was a significant excess was non-Hodgkin lymphoma, and Koda et al.[226] also reported that multiple myeloma was the most frequent malignant tumor occurring in patients on hemodialysis for more than 10 years.

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