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Renal amyloidosis

Correlations between morphology, chemical types of amyloid protein and clinical features

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Summary. Sixty-one autopsy cases of renal amyloidosis were reviewed to assess the relationship of renal pathology to chemical types of amyloid and clinical features. Glomerular amyloid deposition was divided on the basis of morphological characteristics, into four types: a mesangial nodular type showing nodular mesangial deposits with sparse capillary wall involvement (25 cases), a mesangio-capillary type disclosing diffuse amyloid deposition in the mesangium and along both sides of the glomerular basement membrane (19 cases), a perimembranous type principally involving the subepithelial side of the basement membrane invariably characterized by exuberant spicular arrangement (6 cases), and a hilar type showing amyloid deposits almost exclusively in hilar arterioles (11 cases). Twenty-four of 25 cases of mesangial nodular type (96%) showed amyloid protein of AA type. However, mesangio-capillary and perimembranous types were associated with deposition of AL amyloid protein in 15 of 19 (79%) and all 6 cases, respectively. Nephrotic syndrome was more frequent in patients with AL amyloidosis; notably, all patients with perimembranous type had nephrotic syndrome irrespective of the extent of glomerular amyloid deposits. Chronic renal failure and renal death appeared more common in mesangial nodular type in which the extent of glomerular amyloidosis correlated with that of vascular amyloid deposits. The results obtained suggest that the chemical type of glomerular amyloid protein (AA vs AL) is associated with significant differences in the morphological, clinical and prognostic features of the renal involvement.

Key words: Renal amyloidosis – AA and AL proteins – Morphology – Nephrotic syndrome – Renal failure

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Introduction

Renal involvement is very common in systemic amyloidosis (Brandt et al. 1968; Kyle and Bayrd 1975). Traditionally, classification of systemic amyloidosis has been based on the presence (secondary form) or absence of co-existing disorders (primary form). Recent advances in biochemical and immunological studies have demonstrated that at least three different types of amyloid fibril proteins have been identified in the kidney (Glenner 1980; Hill 1983); AA amyloid in secondary or reactive systemic amyloidosis, AL amyloid in patients with primary or myeloma-associated amyloidosis and AF protein relevant to prealbumin in various types of familial amyloidosis.

Until now, many morphological studies have been performed to delineate a variety of details of renal amyloidosis (Watanabe and Saniter 1975; Dikman et al. 1981; Nolting and Campbell 1981; Kemény et al. 1983; Nakamoto et al. 1984). To the best of our knowledge, however, correlation between morphology, chemical types and clinical features of renal amyloidosis has never been adequately evaluated. Such correlations are sought in this study of 61 cases of renal amyloidosis.

Materials and methods

Seventy-five autopsy cases of systemic amyloidosis between 1974–1985 formed the basis of this study. The 61 cases with glomerular amyloid depositions were selected for the present study. There were 25 males and 36 females, ranged in age from 21 to 85 years (average, 59.1 years). Fifty-five cases had been diagnosed as systemic amyloidosis when the patients were alive; in 25 cases of this group this diagnosis was substantiated by biopsies of various organs, including kidney, thyroid, rectum and stomach. In the remaining 6 cases amyloid deposits of various organs including kidneys were incidentally found at autopsy. On the basis of clinical informations the patients were initially divided into three categories; primary (12 cases), myeloma-associated (12 cases) and secondary amyloidosis

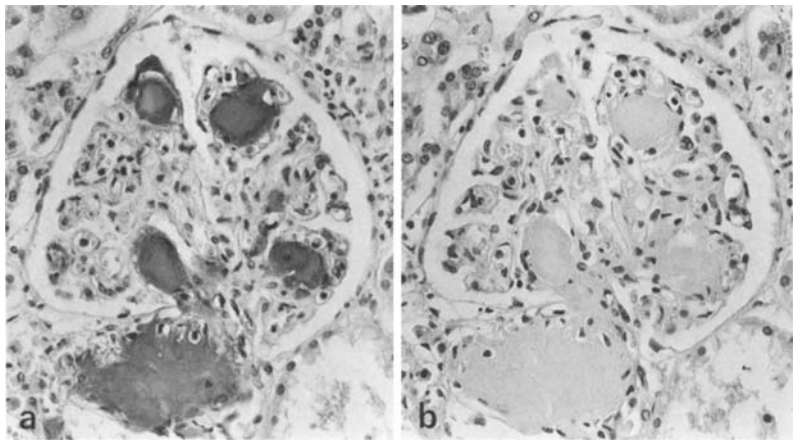

Fig. 1. A glomerulus with amyloid deposits of AA type. **a** Using the PAP method, nodular deposits of amyloid in the mesangium and hilar arteriole are stained positively with anti-AA serum. **b** Staining of a consecutive section with anti-prealbumin serum is negative. Secondary amyloidosis associated with Behçet's disease, 55 year old male. (**a**, **b** ×211)

(37 cases). Among the patients with secondary amyloidosis, chronic inflammatory conditions were found in 34 of 37 cases (92%) with rheumatoid arthritis being the most frequent (25 cases). The remaining 3 cases were associated with malignant tumours.

For light microscopy the renal tissue was stained with haematoxylin-eosin, periodic acid-Schiff (PAS) and Congo red. The presence of amyloid was established by the positive green birefrigence under the polarized light in Congo red-stained sections. In addition, the morphological patterns of amyloid deposits was evaluated from 0.5 μ plastic (Technovit® 7100, Kulzer & Co GmbH, Wehrheim, FRG) embedded sections stained by the Movat's silver method (Watanabe and Saniter 1975).

Histological slides were examined for the severity and morphological pattern of amyloid deposits without prior knowledge of clinical history and chemical types of amyloidosis. The extent of glomerular involvement by amyloid was graded from 1 to 4: grade 1 = amyloid deposits affecting, on an average, less than 25% of the glomerulus, grade 2 = 25–50% of the glomerulus, grade 3 = 50–75% of the glomerulus, grade 4 = more than 75% of the glomerulus. The extent of amyloid deposits in vessels as well as the degree of interstitial fibrosis were assessed simultaneously: 0, absent; 1+, mild; 2+, moderate; 3+, severe.

Two kinds of antisera, anti-AA and anti-prealbumin, were prepared. Prealbumin is antigenically identical to AF protein found in various types of familial amyloidosis (Glenner 1980; Kitamoto et al. 1986). AA protein and prealbumin were purified by the methods previously reported (Kitamoto et al. 1986, 1987), and antisera against each of them were raised in rabbits. Specificity of both antisera was checked by Western blotting (Kitamoto et al. 1986, 1987). The renal tissue was analyzed by peroxidase-antiperoxidase (PAP) methods (Fujiwara et al. 1980; Kitamoto et al. 1987) with anti-AA and anti-prealbumin sera diluted in 1:4000 and 1:2000, respectively. For a comparative evaluation of amyloid protein, potassium permanganate ($KMnO_4$) treatment (Wright et al. 1977) was performed before staining with alkaline Congo red.

AA protein was identified by positive staining with anti-AA serum (Fig. 1), and showed negative staining with anti-prealbumin serum and sensitive to $KMnO_4$ reaction, while AL protein stained negatively with anti-AA and anti-prealbumin sera, and was resistant to $KMnO_4$ reaction.

The following five clinical variables were selected for tabulation; proteinuria, nephrotic syndrome, hypertension, chronic renal failure and renal death.

The nephrotic syndrome was defined as massive proteinuria more than 3.5 g/day, albuminemia less than 3 g/dl. Serum creatinine values more than 2.0 mg/dl were regarded as chronic renal failure. Cases with haemodialysis were counted as renal death. Hypertension was defined as a systolic blood pressure higher than 150 mmHg and a diastolic value more than 95 mmHg.

Table 1. Correlation of clinical, immunohistochemical and histochemical classification of 61 cases of amyloidosis

Staining method	Clinical classification			
	Primary	Myeloma-associated	Secondary	Total
No. of cases	12	12	37	61
Anti-AA:				
positive	0	0	36	36
negative	12	12	1*	25
Anti-prealbumin:				
positive	0	0	0	0
$KMnO_4$ reaction:				
sensitive	1	1	36	38
resistant	11	11	1*	23

* same case

Results

According to the results of PAP methods there were 36 cases of AA amyloidosis and 25 cases of AL amyloidosis (Table 1). Good correlation was noted between clinical classification and the expected amyloid type except for one case. This case clinically classified as secondary amyloidosis associated with rheumatoid arthritis unexpectedly showed deposition of AL protein as evidenced by a negative stain for anti-AA serum and resistance to $KMnO_4$ reaction. There were two cases showing discrepancy between the results of immunohistochemical and histochemical methods. These cases,

Table 2. Morphological types of glomerular amyloidosis related to chemical types of amyloid protein

Morphological type	Amyloid protein	
	AA	AL
I. Mesangial nodular	24	1
II. Mesangio-capillary	4	15
III. Perimembranous	0	6
IV. Hilar	8	3
Total	36	25

one of which is primary and the other, myeloma-associated amyloidosis, showed no staining with anti-AA serum, yet displayed loss of congophilia after $KMnO_4$ treatment.

Silver-stained semithin sections provided excellent details of the morphology and distribution of amyloid in the glomeruli. These findings allowed classification of the 61 cases into four types as summarized in Table 2.

Type I (mesangial nodular): nodular accumulation of amyloid was conspicuous in the mesangium, while capillary walls were sparsely affected (Fig. 2a). Morphological expression of this type was reminiscent of diabetic nodular lesion.

Type II (mesangio-capillary): amyloid deposits spread out diffusely not only in the mesangium but also in the inner as well as outer aspects of the capillary walls (Fig. 2b).

Type III (perimembranous): amyloid deposition principally involved the epithelial side of the basement membrane often showing exuberant spicular arrangement, whereas affection of the mesangium and inner aspect of the capillary wall was inconspicuous (Fig. 2c). Spicules along the glomerular capillary walls often mimicked the spikes in membranous glomerulonephritis (Fig. 3a).

Type IV (hilar): accumulation of amyloid was seen almost exclusively in the hilar arterioles of the glomerulus (Fig. 2d).

It seemed noteworthy that in most cases the glomerular amyloid pattern was similar throughout an individual kidney.

The correlation between the glomerular amyloid patterns and chemical types of amyloid protein is shown in Table 2. It was noticeable that the Type I, mesangial nodular pattern revealed deposition of AA protein in 24 of 25 cases (96%), whereas the Type III, perimembranous pattern, disclosed deposition of AL protein in all 6 cases. One exceptional case with AL amyloidosis in Type I was that concomitantly accompanied by rheumatoid arthritis and AL amyloidosis, as mentioned previously. In addition, Type II, the mesangio-capillary pattern, showed AL deposits in 15 or 19 cases (79%), while in Type IV, the hilar pattern, AA protein was observed in 8 of 11 cases.

Among other glomerular alterations, spicular arrangement of amyloid in the glomerular capillary walls was worthy to note. Spicules, defined as "hair-like" or "comb-shaped" projections radiating outward from the glomerular basement membrane (Ansell and Joekes 1972; Watanabe and Saniter 1975; Moorthy and Burkholder 1977; Nolting and Campbell 1981), were observed by the silver stained sections (Figs. 2a–c, 3) in 34 of 61 cases (56%), including 12 of 25 Type I cases (48%), 16 of 19 Type II cases (84%), all 6 cases of Type III and none of 11 Type IV cases. Cases with Type III invariably revealed florid spicular formations. In general, spicules appeared more commonly in AL amyloidosis (18 of 25 cases, 72%) than in AA amyloidosis (16 of 36 cases, 44%).

With the accumulation of amyloid the basement membrane often lost its affinity for silver compounds (Figs. 2a, 4). Discrete foci of decreased argyrophilia were thus commonly demonstrated in some portions of the basement membrane even in cases with mild glomerular changes. Abrupt breakdown of the basement membrane was less common and only found in isolated cases (Watanabe et al. 1983). Formation of argyrophilic membrane was detected in 19 cases on the epithelial and, less frequently, endothelial aspects of nonspicular capillary wall amyloid (Fig. 4). This new basement membrane formation appeared more common in cases with Types I and II than in Type III.

The summary of clinical features related to morphological types of renal amyloidosis is shown in Table 3. Proteinuira was the most common indicator of renal amyloidosis (in 49 of 60 cases, 82%). It was more frequent in Types I, II and III than Type IV (83, 95, 100, 45%, respectively).

Thirty percent of the patients developed nephrotic syndrome during the clinical course. The occurrence of nephrotic syndrome in Type II roughly paralleled the extent of glomerular amyloid deposits. Type III showed the highest incidence of nephrotic syndrome; it was worthy to note that all 6 cases in this type presented with nephrotic syndrome regardless of the extent of amyloid deposits in glomeruli. In connection with other glomerular alterations, spicular arrangement of amyloid was encountered in 14 of 18 cases (78 %) with nephrotic syndrome; of 14 cases with positive spicular formation 13 cases belonged to

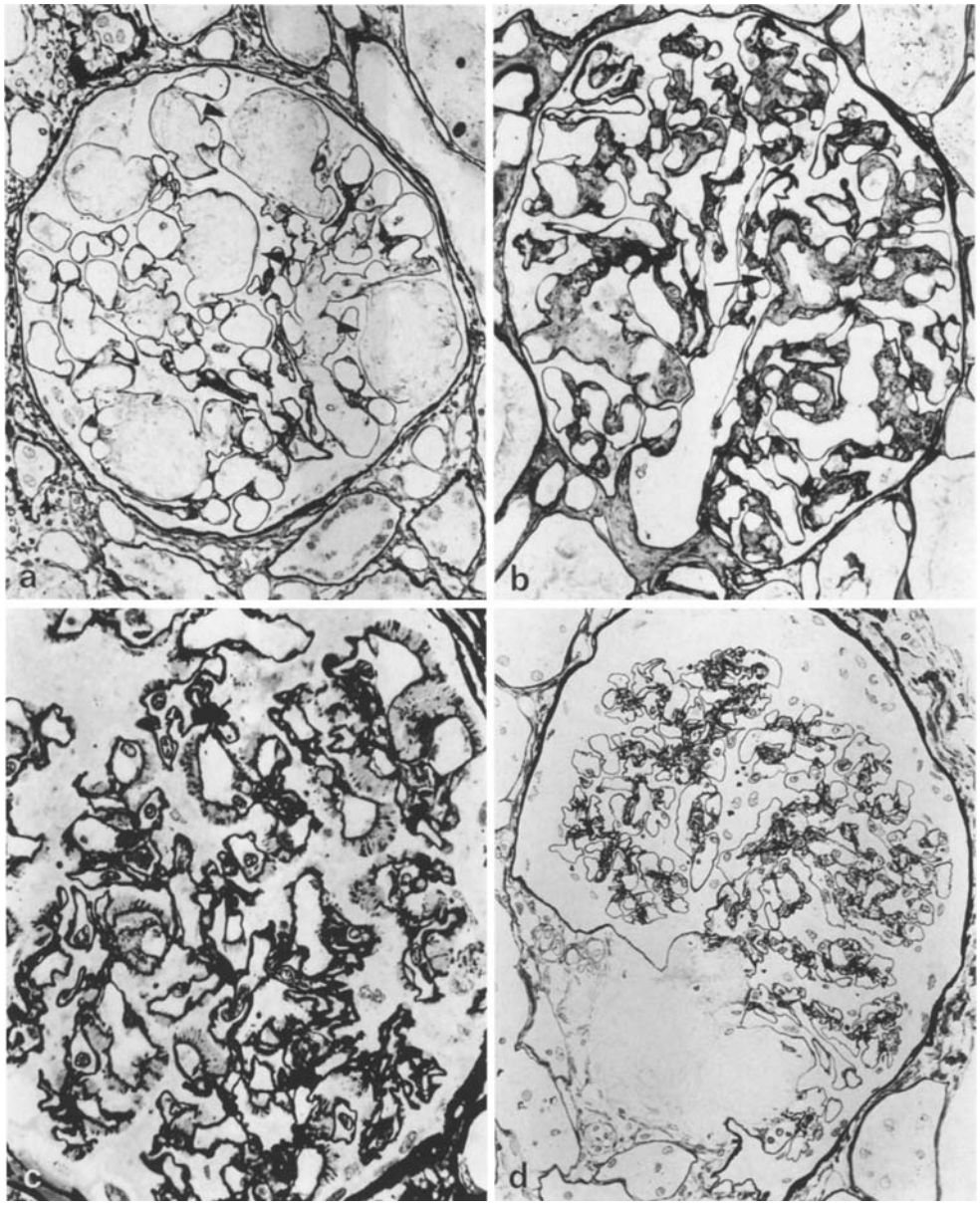

Fig. 2. Morphological patterns of glomerular amyloidosis. **a** *Type I* (mesangial nodular type): amyloid deposits forming nodules in the mesangium. Basement membrane shows a decrease in argyrophilia in relation to amyloid deposits (*arrowheads*). Spicules are evident (*arrow*). AA amyloidosis associated with long standing rheumatoid arthritis, 37 year old female. **b** *Type II* (mesangiocapillary type): amyloid deposits extending from the mesangium to inner as well as outer aspects of the capillary wall. Arrow indicates spicular formation. Primary AL amyloidosis, 56 year old male. **c** *Type III* (perimembranous type): amyloid deposits predominantly involving the outer aspect of the capillary wall. Comb-shaped spicules are conspicuous along the outer aspect of capillary walls. Primary AL amyloidosis, 81 year old female. **d** *Type IV* (hilar type): nodular expansion of the hilar arteriole by amyloid deposits. AA amyloidosis associated with chronic middle otitis, 46 year old female. (Movat's silver staining, **a** ×211; **b** ×233; **c** ×488; **d** ×256)

AL amyloidosis and one was a patient with AA amyloidosis of Type I, whereas the remaining 4 negative cases were patients with AA amyloidosis of Type I.

Chronic renal failure and renal death were seen in 57% and 32% of cases, respectively, and appeared to be more frequent in Type I. Both findings correlated roughly with the extent of glomerular deposits.

Hypertension was present in 32% of cases and showed no apparent difference among the morphological patterns.

The relationship between the extent of glomerular and vascular amyloid deposition is shown in

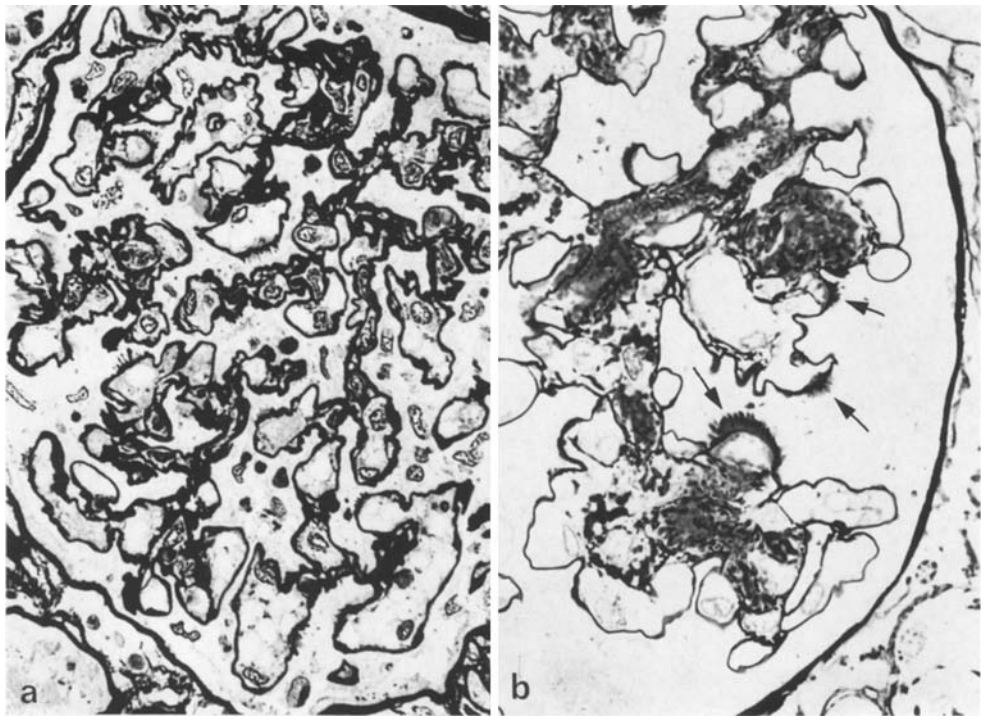

Fig. 3. Amyloid spicules. **a** Fine argyrophilic spicules projecting outward from the capillary wall resembling the spikes in membranous glomerulonephritis. Primary AL amyloidosis, 61 year old female. **b** Typical argyrophilic spicules arranged in comb-shaped appearance (*arrows*). Myeloma-associated AL amyloidosis, 50 year old female. (Movat's silver staining, **a** ×488; **b** ×608)

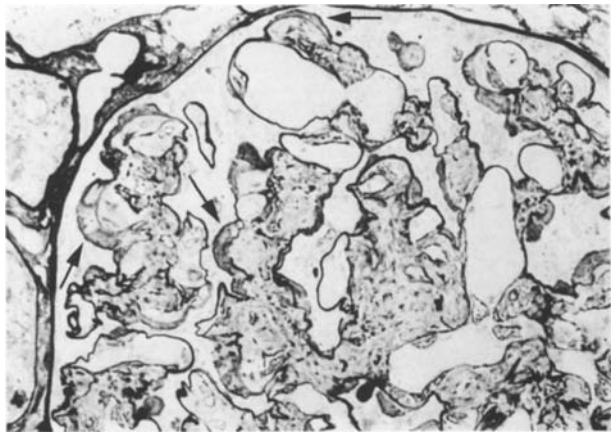

Fig. 4. New formation of the basement membrane structure. Formation of argyrophilic membrane is distinct on the epithelial (*arrows*) aspect of the amyloid. The basement membrane embedded in the amyloid shows loss of argyrophilia. Primary AL amyloidosis, 51 year old male. (Movat's silver staining, ×576)

Table 4. Involvement of blood vessels was observed in all cases. This change was usually more conspicuous in AA amyloidosis often manifesting as Type I, in which the extent of glomerular amyloidosis well correlated to that of vascular deposits. Type II cases showed a similar finding, but the correlation was not significant statistically. Vascular involvement in Type III was less prominent.

Interstitial fibrosis, often accompanied with lymphocytic infiltration, was observed in a number of cases with considerable tubular loss. Amyloid deposition was not infrequently present in the wall of vasa recta and in the interstitium; this occurred much more frequently around the collecting tubules and Henle's loops in the renal medulla than around the proximal tubules.

The relationship between the extent of vascular amyloid, interstitial fibrosis and serum creatinine levels is given in Table 5. It was demonstrated that serum creatinine values significantly correlated to the extent of vascular amyloid and the degree of interstitial fibrosis.

Discussion

A variety of morphological patterns of amyloid within the kidney have been described. Watanabe and Saniter (1975) observed two kinds of distribution patterns of amyloid, nodular and diffuse, in the glomerular capillary networks. Later, Dikman et al. (1981) divided glomerular patterns into four groups, i.e. segmental, diffuse, nodular and mixed nodular-diffuse. As a rare manifestation of amyloid in glomeruli Ansell and Joekes (1972) and Moorthy and Burkholder (1977) reported predominant deposition of amyloid along the capillary

Table 3. Morphological types of renal amyloidosis and clinical features

Morphological type	Proteinuria	Nephrotic syndrome	Hypertension	Chronic renal failure	Renal death
Type I					
grade: 1	5/ 8 (63%)	2/ 8 (25%)	1/ 7 (14%)	4/ 8 (50%)	1/ 8 (13%)
2	2/ 3 (67%)	0/ 3 (0%)	0/ 1 (0%)	3/ 3 (100%)	0/ 3 (0%)
3	9/ 9 (100%)	3/ 9 (33%)	4/ 9 (44%)	9/ 9 (100%)	7/ 9 (78%)
4	4/ 4 (100%)	0/ 4 (0%)	2/ 3 (67%)	4/ 4 (100%)	4/ 4 (100%)
subtotal	20/24 (83%)	5/24 (21%)	7/20 (35%)	20/24 (83%)	12/24 (50%)
Type II					
grade: 1	5/ 6 (83%)	0/ 6 (0%)	3/ 3 (100%)	2/ 6 (33%)	0/ 6 (0%)
2	7/ 7 (100%)	2/ 7 (29%)	0/ 6 (0%)	4/ 7 (57%)	2/ 7 (29%)
3	4/ 4 (100%)	3/ 4 (75%)	0/ 4 (0%)	2/ 4 (50%)	2/ 4 (50%)
4	2/ 2 (100%)	2/ 2 (100%)	1/ 2 (50%)	2/ 2 (100%)	2/ 2 (100%)
subtotal	18/19 (95%)	7/19 (37%)	4/15 (27%)	10/19 (53%)	6/19 (32%)
Type III					
grade: 1	2/ 2 (100%)	2/ 2 (100%)	0/ 2 (0%)	0/ 2 (0%)	0/ 2 (0%)
2	2/ 2 (100%)	2/ 2 (100%)	1/ 2 (50%)	0/ 2 (0%)	0/ 2 (0%)
3	1/ 1 (100%)	1/ 1 (100%)	1/ 1 (100%)	1/ 1 (100%)	1/ 1 (100%)
4	1/ 1 (100%)	1/ 1 (100%)	0/ 1 (0%)	1/ 1 (100%)	0/ 1 (0%)
subtotal	6/ 6 (100%)	6/ 6 (100%)	2/ 6 (33%)	2/ 6 (33%)	1/ 6 (17%)
Type IV	5/11 (45%)	0/11 (0%)	3/ 9 (33%)	2/11 (18%)	0/11 (0%)
Total	49/60 (82%)	18/60 (30%)	16/50 (32%)	34/60 (57%)	19/60 (32%)

No. of positive cases/cases in which data were obtained shown in Table

*$p<0.05$; **$p<0.01$ (Fisher's test)

Table 4. Correlation between the extent of glomerular and vascular amyloid deposition

Morphological type	Grade of glomerular amyloid	Grade of vascular deposition		
		1	2	3
I*	1	2	3	3
	2	0	1	3
	3	0	1	8
	4	0	0	4
II	1	1	3	2
	2	2	1	4
	3	0	2	2
	4	0	0	2
III	1	2	0	0
	2	1	1	0
	3	1	0	0
	4	0	1	0
IV		6	4	1

* correlation coefficient, $r=0.542$ ($p<0.01$)

Table 5. Correlation between the extent of vascular amyloid deposition, interstitial fibrosis and serum creatinine levels

Serum creatinine (mg/dl)	Vascular deposition* grade			Interstitial fibrosis** grade			
	1	2	3	0	1	2	3
Less than 2.0	12	10	4	8	14	3	1
2.0 ~ 5.0	2	6	6	3	7	3	2
more than 5.0	1	1	18	0	1	9	9

* correlation coefficient, $r=0.616$ ($p<0.001$)
** correlation coefficient, $r=0.636$ ($p<0.001$)

loop forming argyrophilic spicules that resembled the histopathologic picture seen in membranous glomerulonephritis. There was also a form of predominantly vascular amyloid deposition in the kidney (Falck et al. 1983). To date, only few reports have formally attempted to correlate the morphological patterns of amyloid in the kidney with chemically defined amyloid types and clinical features. In this context, Dikman et al. (1981) observed that nodular pattern was more common in patients with secondary amyloidosis. However, they did not identify chemical types of amyloid protein. Never-the-less, using the $KMnO_4$ method Kemény et al. (1983) and Nakamoto et al. (1984) found that AL amyloidosis more often disclosed diffuse pattern.

In the present study, we classified glomerular amyloid deposition into four types as mentioned

above. It is well known that in the early phase of amyloidosis glomerular involvement tends to be spotty or segmental, and as amyloid deposits increase in amount, the location and extent of amyloid deposits become more uniform (Hill 1983). This means that, particularly in mild grade 1 amyloidosis, typing of the morphological patterns is not always easy with biopsy materials that contain a limited number of glomeruli. We therefore examined a series of autopsy cases with silver-stained plastic embedded semithin sections to facilitate the determination of morphological patterns of a large number of glomeruli.

The present study suggested a good correlation between morphological patterns and chemical types of amyloidosis. In Type I mesangial nodular pattern, deposited amyloid was almost invariably AA protein. Involvement of blood vessels was generally conspicuous, roughly paralleling with that of the glomeruli. In contrast, the Type III perimembranous pattern always disclosed deposition of AL amyloid with exuberant formation of spicules along the capillary loop. Although Type II mesangio-capillary pattern variably revealed mixed or transitional features in morphology between Types I and III, cases with AL amyloidosis predominated. Type IV hilar pattern was often seen in patients with AA amyloidosis.

The morphological diversity observed in this study strongly suggests different tissue affinities of AA and AL proteins in glomeruli. It seems likely that AA protein has predisposition to deposit in the mesangium and, most conceivably under the influence of mesangial cells, accumulates in nodular fashion. This speculation is supported by the findings by Caesar (1963) and Shirahama and Cohen (1967) in experimentally induced AA amyloidosis, that the mesangial area is the primary area associated with the deposition of amyloid fibrils.

In contrast to AA protein, AL protein tends to deposit more diffusely in the glomeruli. As observed in Type II cases, amyloid deposits of variable size appeared early along the capillary loop often in a form of lateral extension from the mesangium and finally encircled and obliterated the capillary lumen (Watanabe and Saniter 1975). Further, this type of amyloid often showed isolated deposits in glomerular loops without nearby mesangial involvement (Gise et al. 1981; Nolting and Campbell 1981; Katafuchi et al. 1984). In extreme cases, as evidenced by Type III cases, distribution of AL amyloid was confined predominantly to the subepithelial aspect of the capillary wall. Here, amyloid protein radiated outward from the glomerular loops forming a spicular arrangement. As suggested by Thoenes and Schneider (1980), Nolting and Campbell (1981) and Gise et al. (1981), it seems likely that, particularly in AL amyloidosis of Type III, amyloid presursors coming from blood stream are filtered through the capillary wall and react in some way probably with lysosomal enzyme of epithelial cells to form this unique variant of amyloid.

The present study demonstrated that nephrotic syndrome was more frequent in AL amyloidosis, in which the deposition of amyloid along the basement membrane was the predominant feature. As represented by decreased argyrophilia of the basement membrane (Watanabe and Saniter 1975) or the findings by electron microscopy that amyloid fibrils are traversing the lamina densa of this structure (Shirahama and Cohen 1967; Gise et al. 1978; Dikman et al. 1981; Nolting and Campbell 1981; Gise et al. 1981; Katafuchi et al. 1984), such deposition of amyloid may cause severe metabolic and structural damage to the basement membrane and contribute to the escape of plasma protein into the urinary space. In agreement with Dikman et al. (1981) who observed more extensive spicular formations in the cases associated with primary amyloidosis, spicular deposits of amyloid in the present series were more prominent in cases with AL amyloidosis. As shown in Type III cases, patients with prominent spicules often had a florid nephrotic syndrome even when the total amount of glomerular amyloid was small. This confirms the previous reports (Gise et al. 1978; Katafuchi et al. 1984) that massive loss of serum protein may occur at the places where amyloid fibrils are arranged in spicules which are invariably associated with detachment or foot process loss of epithelial cells.

This study confirmed the findings of the previous investigators (Watanabe and Saniter 1975; Mackensen et al. 1977) that the amount of glomerular amyloid roughly correlated with rising serum creatinine. Further, renal insufficiency and renal death appeared more common in cases with Type I glomerular lesion in which the extent of glomerular amyloid well correlated with that of vascular amyloid, which in turn significantly correlated with serum creatinine concentrations just as the degree of interstitial fibrosis did.

Mackensen et al. (1977), using morphometric technique, first reported that renal failure developed mainly as a result not only of glomerular amyloid but also of interstitial fibrosis. Later, Törnroth et al. (1980) observed that the degree of vascular amyloidosis and interstitial fibrosis correlated with the rate of clinical progression of renal insufficiency. It may be assumed that narrowing

and occlusion of vessels by amyloid deposition in the vessel walls cause ischemia, which results in fibrosis and loss of nephrons (Brandt et al. 1968; Törnroth et al. 1980). Compared with AL amyloidosis, amyloid deposits in vessel walls were generally more prominent in AA amyloidosis. This is in accord with the findings of some recent authors (Falck et al. 1983; Iwata and Ishihara 1985) but is opposed to those of others (Pirani 1976; Hill 1983) noting that primary and myeloma-associated amyloidosis affects the vessels predominantly. Falçk et al. (1983) have reported a series of cases with secondary amyloidosis with predominantly vascular but minimal or no glomerular amyloid deposition and stressed that even such cases often presented signs of renal insufficiency. Although a morphological explanation for decreased renal function is not always possible, it seems likely that impairment of renal function is caused by combined effects of glomerular, vascular and interstitial factors. The contribution of these variables may be variable from case to case. It is our impression that vascular involvement by amyloid is often important in cases with AA amyloidosis.

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