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Original Article

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Rapidly Progressive Renal Failure in AA Amyloidosis: A New Clinical and Histopathological Entity for an Old Disease

Zeynep Kendi Çelebi[1], Saba Kiremitçi[2], Rezzan Eren Sadioğlu[3], Kenan Keven[3]

[1]Department of Nephrology, Başkent University School of Medicine, Ankara, Turkey
[2]Department of Pathology, Ankara University School of Medicine, Ankara, Turkey
[3]Department of Nephrology, Ankara University School of Medicine, Ankara, Turkey

Abstract

Objective: Secondary renal AA amyloidosis (RAAA) presents with proteinuria and/or as nephrotic syndrome and progresses to end stage renal disease (ESRD) insidiously. However, some patients with secondary amyloidosis show a more rapid renal disease progression than the usual course. In this study, we aimed to investigate the underlying cause of the rapidly progressive renal disease in the patients with secondary amyloidosis.
Materials and Methods: Patients with kidney biopsy proven secondary RAAA were divided into 2 groups: the rapidly progressive group (estimated glomerular filtration rate >60 mL/min, who needed renal replacement therapy within one year of diagnosis) and the control group. Biopsy specimens were reevaluated for glomerular-vascular amyloid load, tubular atrophy, interstitial fibrosis, and interstitial inflammation. The biopsy characteristics and biochemical parameters were compared between the groups.
Results: Histopathological examination showed global amyloid deposition, vascular pole involvement, peritubular capillary amyloid deposition, and severe interstitial inflammation associated with rapidly progressive disease. Estimated glomerular filtration rate was lower and proteinuria was higher in the rapidly progressive group than in the control group. Vascular pole amyloid deposition was found to be a predictor of ESRD in multivariate analysis.
Conclusion: This study shows that higher amyloid deposition and severe inflammation revealed in in kidney biopsy of secondary RAAA cases can be risk factors for rapidly progressive renal failure.
Keywords: Amyloidosis, biopsy, kidney, kidney failure

Corresponding Author: Zeynep Kendi Çelebi ✉ zeynepkendi@yahoo.com
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INTRODUCTION

Renal AA amyloidosis (RAAA) is a rare cause of chronic renal failure. However, the etiology of RAAA is geographically distributed, and familial Mediterranean fever (FMF) is the most common cause in Turkey, while rheumatoid arthritis, chronic inflammatory bowel diseases, and chronic infections such as bronchiectasis, osteomyelitis, and tuberculosis can also cause secondary amyloidosis. The prevalance of AA amyloidosis in hemodialysis patients is 1.76% in Turkey (1).

Renal involvement in AA amyloidosis is a determinant of the disease course, and it can manifest either with asymptomatic proteinuria or as nephrotic syndrome. The course of the renal disease in secondary amyloidosis is considered to be slow. Previous studies have reported that approximately 10 years or more are needed for the development of end stage renal disease (ESRD) after diagnosis of AA amloidosis (2). The disease has also been noted to recur 7-8 years after kidney transplantation (2-4).

In our clinical experience, we have observed that some patients with secondary RAAA have a very rapid deterioration of renal functions without any identified cause. This study aimed to find a histopathological or biochem-

ical marker that could be a predictor of rapid deterioration of renal functions in such cases.

MATERIALS AND METHODS

A total of 57 patients who were admitted to our nephrology clinic and diagnosed with RAAA by renal biopsy between 2005 and 2019 were retrospectively evaluated. Patients with primary amyloidosis, those with ESRD at admission, those with a follow-up of less than 12 months, or patients diagnosed with AAA through other biopsies (abdominal fat tissue, bone marrow, or duodenal biopsy) were excluded from the study.

Rapid deterioration in renal function was defined as the need for renal replacement therapy within 1 year of diagnosis in patients with a baseline estimated glomerular filtration rate (eGFR) above 60 mL/min/1.73 m^2. Blood urea nitrogen (BUN), creatinine, albumin, uric acid, sedimentation, C-reactive protein, ferritin, urinary protein excretion (24 hour urine protein), lipid profile, and eGFR were recorded at admission and at follow-up visits. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Renal biopsy specimens were reevaluated by 2 renal pathologists. Biopsy samples with fewer than 8 glomeruli were not included in the study. The sections stained with haematoxylin-eosin, periodic acid-Schiff, Masson's trichrome, methenamine silver, and Congo red stains were evaluated. All immunofluorescence examinations were negative for IgG, IgA, IgM, C3, C1q, fibrinogen, kappa, and lambda. Amyloid deposition patterns were noted as hilar, mesengial, nodular, and membranous as defined in previous studies. The nodular accumulation of amyloid, which defines the large nodular mesangial deposits compressing the peripheral part of the tuft, was also noted. The glomerular amyloid load was scored as segmental (amyloid deposition involving <50% of one glomerulus) or global (amyloid deposition involving >50% of one glomerulus). The extent of glomerular amyloid deposition was scored as focal (involvement of <50% of total glomeruli in the whole biopsy specimen) or diffuse (involvement of >50% of total glomeruli in the whole biopsy specimen) according to the glomerular percentage. The number of the glomeruli showing global collapse of capillary lumens due to amyloid deposition (glomerular obliteration) was also recorded (5, 6).

Main Points

- Systemic amyloidosis is caused by misfolding and extracellular deposition of one of an ever-growing list of circulating proteins, resulting in vital organ dysfunction and eventually death.
- We experienced that some of our patients with renal AA amyloidosis showed a very rapid detoriation in renal function and needed renal replacement therapy.
- The presence of hilar pattern in histopathology, global involvement due to amyloid deposition in the glomeruli and the accompanying severe interstitial inflammation accelerated the progression of renal disease in these patients.

Statistical Analysis

IBM Statistical Package for Social Sciences version 22.0 software (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. Parametric data were presented as mean±standard deviation. The Chi-squared test was used to compare ordinal variables. Student's t-test was used for parametric variables, and the Mann-Whitney U test was used for nonparametric variables. The Spearman and Pearson tests were used for correlation analysis. Multivariate analyses were performed by logistic regression. A threshold value of $p<0.05$ was considered to be significant.

RESULTS

RAAA patients were divided in 2 groups and examined. The first group included 12 patients with rapid detoriation in renal function, and the control group included 11 patients who were age- and sex-matched with stable renal function.

In the study group, 3 patients had FMF, 1 had rheumatoid arthritis, 1 had hydradenitis suppurutiva, and 1 had bronchiectasis as AAA etiology. The etiological cause could not be determined in 6 patients. In the control group, 1 patient had bronchiectasis and 8 patients had FMF. The etiology was not detected in 2 patients. All the patients received colchicine treatment, except 3 patients who were newly diagnosed with AA amyloidosis (2 patients in the study group, 1 patient in the control group) and 4 patients who were incompatible with the treatment (2 patients in the study group, and 2 patients in the control group). There was no difference in the use of colchicine between the rapidly progressing group and the control group (p=1.000). There were no patients using biological agents for amyloidosis.

The mean age of patients in the rapidly progressive group was 60±10 years and 52±12 years in the control group (p=0.123).

At follow-up, all the patients in the rapidly progressive group had developed ESRD 6±4 months after the kidney biopsy. Mean follow-up time of both the groups was 25±16 months.

Baseline biochemical parameters of the patients are given in Table 1. The group with rapidly progressive amyloidosis showed lower eGFR and hemoglobin and higher proteinuria levels (p=0.043, p=0.017, and p=0.028, respectively). Albumin, uric acid, erythyrocyte sedimentation rate, c-reactive protein, and lipid levels were similar in both the groups (p>0.05).

The mean glomeruli number in the biopsy specimens was 19±11. The amyloid deposition patterns and the features of chronic renal damage markers are given in Table 2 and Table 3. Pathological examination of kidney biopsies showed a more hilar pattern and global amyloid involvement in the rapidly progressive amyloidosis group (p=0.007, p=0.001), but less peritubular capillary amyloid deposition (p=0.035). There was no significant difference between the groups in terms of interstitial fibrosis and tubular atrophy, where as more and severe inter-

Table 1. Baseline biochemical parameters of the rapidly progressive amyloidosis and the control groups

	Rapidly progressive amyloidosis (n=12)	Control group (n=11)	p
Creatinine (mg/dL)	1.18±0.21	0.91±0.39	0.051
eGFR (mL/min/1.73 m^2)	67±9	89±32	0.043*
Proteinuria (g/day, 24-hour urine)	14.3±10.6	6±4.7	0.028*
Total protein (g/dL)	5.08±1.16	5.5±1.03	0.230
Albumin (g/dL)	2.15±0.88	2.71±0.88	0.142
Hemoglobin (g/dL)	10.9±1.7	13.1±2.2	0.017*
Uric acid (mg/dL)	6.7±2.1	6.1±1.5	0.440
CRP (mg/dL)	46±43	43±40	0.923
ESR (mm/h)	82±41	68±40	0.420
LDL (mg/dL)	181±69	183±85	0.852
Total cholesterol (mg/dL)	262±99	270±110	0.738

*statistically significant
eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDL: low density cholesterol

Table 2. Amyloid deposition characteristics in kidney biopsy specimens

	Rapidly progressive amyloid (n=12)	Control group (n=11)	p
Glomerular enlargement (n, %)	8 (66.6)	4 (15.9)	0.146
Glomerular-vascular pole amyloid deposition, “Hilar pattern” (n, %)	10 (83.3)	3 (27.2)	0.007*
Glomerular mesengial amyloid deposition “Mesengial pattern” (n, %)	12 (100)	11 (100)	
Nodular amyloid deposition, “Nodular pattern” (n, %)	6 (50)	6 (54.5)	0.827
Glomerular basement membrane involvement, “Membranous pattern” (n, %)	11 (91.6)	8 (72.7)	0.231
Glomerular amyloid load-global involvement, (involving >50% of a glomerulus), (n, %)	12 (100)	4 (15.9)	0.001*
Diffuse glomerular amyloid deposition (n, %)	12 (100)	9 (81.8)	0.122
Amyloid deposition in interstitium (n, %)	6 (50)	7 (63.6)	0.342
Tubular basement membrane involvement (n, %)	6 (50)	3 (33.3)	0.342
Peritubular capillary amyloid deposition (n, %)	3 (25)	7 (70)	0.035*
Foamy cells in interstitium (n, %)	2 (16.6)	2 (18.11)	0.924
Arteriolar wall involvement (n, %)	12 (100)	11 (100)	
Mesengial amyloid deposition (n, %)	12 (100)	11 (100)	

*statistically significant

Table 3. Severity of chronic renal damage and distribution of cases

		None	Mild	Moderate	Severe	p
Interstitial fibrosis	Rapidly progressive amyloid group (n, %)	0	5 (41.6)	6 (50)	1 (8.3)	0.058
	Control group (n, %)	5 (45.4)	3 (27.3)	3 (27.3)	0	
Tubular atrophy	Rapidly progressive amyloid group (n, %)	0	4 (25)	7 (58.3)	1 (8.3)	0.052
	Control group (n, %)	5 (45.4)	3 (27.3)	3 (27.3)	0	
Interstitial inflammation	Rapidly progressive amyloid group (n, %)	0	5 (41.6)	3 (25)	4 (25)	0.024*
	Control group (n, %)	5 (45.4)	3 (27.3)	3 (27.3)	0	

*statistically significant

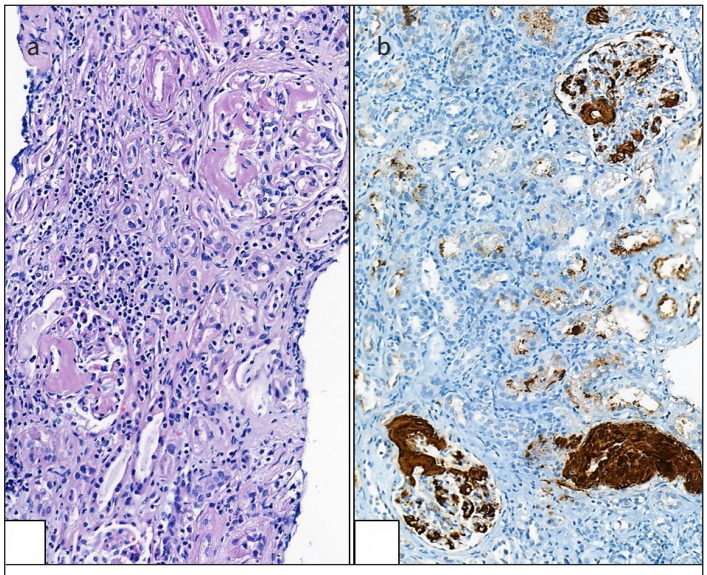

Figure 1. a, b. a) Glomerular amyloid deposition in mesangium and vascular pole and tubulointerstitial inflammation (hematoxylin&eosin, 211x). b) Amyloid A positivity in mesangium and vascular pole of the glomeruli (immunohistochemistry, 167x)

stitial inflammation was observed in the rapidly progressive amyloidosis group. There was no relationship between global and vascular pole amyloid deposition (p=0.650). The results of patients with and without global amyloid accumulation are given in Table 4. Obliterated glomeruli number were significantly higher in patients with global amyloid deposition compared to those with segmental amyloid deposition. On the other hand, eGFR and hemoglobine levels were significantly lower in patients with global amyloid deposition.

Figure 1 shows the hilar pattern and severe interstitial inflammation in the kidney biopsy specimen.

Patient characteristics according to proteinuria levels and vascular pole involvement are given in Tables 5 and 6.

Biopsy specimens showing hilar pattern also had higher degrees of interstitial inflammation (p=0.042).

Multivariate analysis of the biopsy characteristics including the hilar pattern, interstitial inflammation, and peritubular capillary amyloid deposition showed that the hilar pattern was the only risk factor for developing rapidly progressive amyloidosis and ESRD. Results are given in Table 7.

At follow-up, 1 patient had died because of sepsis and 2 patients with FMF had had a kidney transplant from a living-related donor. These patients have shown no evidence of amyloidosis recurrence after 5 years of transplantation. One of these patientsrecieved colchicin and the other anakinra.

DISCUSSION

In this study, we reported on a subgroup of RAAA patients with rapidly progressing and developing ESRD. This entity has both histopathological and clinical properties. Histopathological characteristics of this subgroup include a more frequent hilar pattern and global involvement of glomerulus, fewer peritubular capillary amyloid depositions, and more severe interstitial inflammation than in the control group. These patients also had lower eGFR and hemoglobin levels and higher proteinuria levels.

The rapid progression pattern was first described in 1994 by Livneh et al. (7); however, in this FMF-associated amyloidosis group, there were conditions such as pneumonia and diarrhea that could affect renal function. With this study, we were the first to identify this rapidly progressive group without an obvious cause of acute kidney injury.

In our study, baseline eGFR levels were lower in the rapidly progressive group than in the control group. Higher creatinine and lower eGFR levels were associated with ESRD development. In the previous studies, a creatinine value above 1.5 mg/dL or eGFR below 60 mL/min/1.73 m^2 was reported as a risk factor (8,

Table 4. Global amyloid deposition and biochemical parameters

Parameter	Global amyloid deposition (n=16)	Segmental amyloid deposition (n=7)	p
Creatinine (mg/dL)	1.3±0.6	0.8±0.2	0.068
eGFR (mL/min/1.73 m^2)	61±33	93±21	0.029*
Hemoglobine (g/dL)	10.8±1.6	14.4±1.3	<0.001
Uric acid (mg/dL)	6.6±1.9	6±1.6	0.456
Albumine (g/dL)	2.3±0.8	2.7±0.9	0.347
ESR (mm/h)	87±38	50±34	0.041*
Proteinuria (g/day, 24 hour urine)	12±10	6±5.5	0.192
Hilar pattern (n, +/-)	10/6	3/4	0.650
Obliterated glomeruli number (%)	2±3	0.2±0.5	0.047*

*statistically significant
eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate

Table 5. Biochemical parameters according to proteinuria levels

Parameter	Nephrotic syndrome (n=16)	Nonnephrotic proteinuria (n=7)	p
Creatinine (mg/dL)	1.2±0.6	1.1±0.4	0.737
eGFR (mL/dk/1.73 m^2)	73±34	66±31	0.678
Hemoglobine (g/dL)	11.6±2.3	12.7±2	0.293
Uric acid (mg/dL)	6±1.8	7.5±1.5	0.067
Albumine (g/dL)	2.04±0.6	3.2±0.8	0.001*
ESR (mm/h)	92±33	40±31	0.03*
Proteinuria (g/day, 24 hour urine)	14.3±8.2	1.3±1	0.001*
Rapidly progressive amyloidosis/control group (n,%)	9/7 (56/44)	3/4 (42/58)	0.667

*statistically significant
eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate

9). However, in our study, although the creatinine values of the rapidly progressive group were lower than 1.5 mg/dL and eGFR levels were higher than 60 mL/min/1.73 m^2, end stage renal failure developed in approximately 6 months. This result suggests that factors other than baseline kidney functions are responsible for this rapid progression.

Proteinuria is a well-defined risk factor for chronic kidney disease and is also identified as a risk factor in the course of amyloidosis (10-12). A patient's clinical presentation is influenced by the localization of the amyloid protein. Glomerular amyloid deposition results in proteinuria, whereas tubulointerstitial or vascular involvement is mainly associated with renal failure (13). In different studies, it has been reported that the annual GFR loss varies between 1.03 and 5 mL/min/1.73 m^2 in patients with different etiologies and whose GFR levels were below 60 mL/min/1.73 m^2 (14, 15). Although the baseline eGFR level was higher than 60 mL/min/1.73 m^2 in our study group, the need for renal replacement therapy occurred in 1 year. Proteinuria as a known risk factor, and our patients with rapid progression also had massive proteinuria compared to the control group, and pathological amyloid accumulation occured in both glomerular and vascular compartments. We could not show a relationship between global amyloid accumulation and the presence of the

Table 6. Biochemical parameters and characteristics of patients with or without hilar pattern

Parameter	Patients with vascular pole amyloid deposition (n=13)	Patients without vascular pole amyloid deposition (n=10)	p
Age (years)	59±11	44±12	0.046*
Systolic blood pressure (mm Hg)	115±21	137±22	
Diastolic blood pressure (mm Hg)	64±6	88±11	0.001*
Creatinine (mg/dL)	1.3±0.6	0.9±0.4	0.111
eGFR (mL/min/1.73 m^2)	60±27	84±36	0.085
Hemoglobine (g/dL)	11.4±2	12.6±2.4	0.204
Uric acid (mg/dL)	7.1±2	5.6±1.3	0.047*
Albumine (g/dL)	2.2±0.9	2.6±0.8	0.331
ESR (mm/h)	83±4	66±38	0.359
Proteinuria (g/day, 24 hour urine)	12±9.9	8.1±7.9	0.059
CRP (mg/dL)	64±30	19±13	0.05*

*statistically significant
eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimantation rate; CRP: C-reactive protein

Table 7. Multivariate analysis of biopsy parameters for rapidly progressive amyloidosis

Parameter	p	Odds ratio	95% CI (lower-upper)
Hilar pattern	0.029	23.418	1.386-395.801
Interstitial inflammation	0.097	0.187	0.26-1.358
Peritubular capillary amyloid deposition	0.314	0.252	0.017-3.699

hilar pattern in our study; therefore, vascular pole involvement could not be explained by the extensiveness of amyloid accumulation. Furthermore, the presence of the hilar pattern was found to be a pathologically independent risk factor. More studies are needed to explain the rapid decline in eGFR in patients with amyloidosis.

We have stated that the hilar pattern was associated with worse renal outcomes. In a histopathological study by Verine et al. (16), the hilar pattern was described as being predominantly vascular amyloid deposition, less in glomerular space, and especially at the vascular pole; the relationship between glomerular involvement and proteinuria was also shown. This study also showed that the arteriolar amyloid load was associated with lower creatinine clearence levels. In our study, we could not show any relationship between proteinuria and histopathological parameters because all of our patients had arteriolar wall amyloid accumulation; but our patients with global amyloid deposition also had lower eGFR levels as in this study (16). Our rapidly progressive group had both global glomerular involvement and hilar pattern. Therefore, these patients may have had very high levels of proteinuria.

Although there was no significant difference between the groups in terms of interstitial fibrosis and tubular atrophy, which are signs of chronic kidney injury, more and severe interstitial inflammation was observed in the rapidly progressive amyloidosis group. The intrarenal renin-angiotensin-aldosterone system may be activated by global amyloid deposition and related interstitial inflammation, especially in patients with the hilar pattern, by influencing the juxtaglomerular apparatus. Studies have shown that the urinary angiotensinogen level is increased in AAA patients, and this increase may cause accelerated fibrosis and rapid detoriation in kidney functions that are revealed at follow-up (17, 18). Our study group had global amyloid deposition in glomerulus and massive proteinuria. Although not statistically significant, Ueno et al. (19) showed that patients with amyloidosis secondary to rheumatoid arthritis, who respond to treatment with DMARD (disease-modifying antirheumatic drugs) and biological agents, had higher amyloid deposition in the glomerulus and interstitial

inflammation and higher proteinuria than the nonresponders. In the same study, a control kidney biopsy was performed in 1 patient at follow-up, and the biopsy specimen showed no decrease in amyloid burden but decreased inflammation and improved foot process effacement of podocytes. At follow-up, these patients with high amyloid deposition had decreased levels of proteinuria and creatinine after appropriate treatment for the primary disease and blood pressure control (19). Similarly, in another patient with ankylosing spondylitis, it was observed that the accompanying interstitial inflammation decreased significantly, and the effacement of the foot processes improved without any significant change in amyloid accumulation in the control kidney biopsy performed after antiTNF treatment (20).

AA amyloidosis results from the deposition of the serum amyloid A protein (SAA) in chronic inflammatory states. This protein promotes fibrillogenesis, resists degradation and accumulates in the tissue, resulting in organ dysfunction (21). Interstitial inflammation is not an expected pathologic feature in the diagnosis of AA amyloidosis. Studies on the inflammation in AA amyloidosis are mainly about systemic inflammation, and treatment is given to control systemic inflammation. The cause of the interstitial inflammation may not be attributed to the amyloid protein itself, but may be associated with cytokines that are released owing to tissue damage caused by the accumulation of the amyloid protein. More studies are needed to delineate this aspect.

Our study had several limitations. First, the number of patient groups were small. Because secondary amyloidosis is a rare disease, and patients are referred to the nephrology clinic only in the presence of proteinuria or increased levels of creatinine, and the diagnosis of amyloidosis can be made with tissue samples from organs other than the kidney, the number of renal biopsies is limited. Second, we were not able to measure the SAA levels. There is evidence that SAA levels correlate with disease activity and may also have a significant relationship with pathological classification (22). Third, the etiologies for AAA for some of our patients were not identified. This nonhomogenity probably affects the pathologic characteristics.

CONCLUSION

We have described a new entity for secondary amyloidosis, i.e., rapidly progressive AAA. This patient group needs detailed investigation and probably needs aggressive treatments, such as biological agents, to control inflammation in addition to colchicine.

Ethics Committee Approval: Ethics committee approval was not received for this study.

Informed Consent: Informed consent was not obtained due to the nature of this study.

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