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Original article

Clinical outcomes and survival in AA amyloidosis patients

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ABSTRACT

Aim: Amyloid A amyloidosis is a rare complication of chronic inflammatory conditions. Most patients with amyloid A amyloidosis present with nephropathy and it leads to renal failure and death. We studied clinical characteristics and survival in patients with amyloid A amyloidosis.

Methods: A total of 81 patients (51 males, 30 females) with renal biopsy proven amyloid A amyloidosis were analyzed retrospectively. The patients were divided into good and poor outcomes groups according to survival results.

Results: Most of the patients (55.6%) had nephrotic range proteinuria at diagnosis. Most frequent underlying disorders were familial Mediterranean fever (21.2%) and rheumatoid arthritis (10.6%) in the good outcome group and malignancy (20%) in the poor outcome group. Only diastolic blood pressure in the good outcome group and phosphorus level in the poor outcome group was higher. Serum creatinine levels increased after treatment in both groups, while proteinuria in the good outcome group decreased. Increase in serum creatinine and decrease in estimated glomerular filtration rate of the poor outcome group were more significant in the good outcome group. At the time of diagnosis 18.5% and 27.2% of all patients had advanced chronic kidney disease (stage 4 and 5, respectively). Median duration of renal survival was 65 ± 3.54 months. Among all patients, 27.1% were started dialysis treatment during the follow-up period and 7.4% of all patients underwent kidney transplantation. Higher levels of systolic blood pressure [hazard ratios 1.03, 95% confidence interval: 1–1.06, $p = 0.036$], serum creatinine (hazard ratios 1.25, 95% confidence interval: 1.07–1.46, $p = 0.006$) and urinary protein excretion (hazard ratios 1.08, 95% confidence interval: 1.01–1.16, $p = 0.027$) were predictors of end-stage renal disease. Median survival of patients with organ involvement was 50.3 ± 16 months.

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Conclusion: Our study indicated that familial Mediterranean fever constituted a large proportion of cases and increased number of patients with idiopathic amyloid A amyloidosis. Additionally, it was observed that patient survival was not affected by different etiological causes in amyloid A amyloidosis.

Desfechos clínicos e sobrevida em pacientes com amiloidose AA

Palavras-chave:
Amiloidose AA
Doença renal crônica
Febre familiar do Mediterrâneo
Mortalidade
Sobrevida renal

RESUMO

Objetivo: A amiloidose AA é uma complicação rara de condições inflamatórias crônicas. A maior parte dos pacientes com amiloidose AA apresenta nefropatia, que leva à insuficiência renal e à morte. Estudaram-se as características clínicas e a sobrevida em pacientes com amiloidose AA.

Métodos: Analisaram-se retrospectivamente 81 pacientes (51 homens, 30 mulheres) com amiloidose AA comprovada por biópsia renal. Os pacientes foram divididos em grupos de desfecho bom e ruim de acordo com os resultados de sobrevida.

Resultados: A maior parte dos pacientes (55,6%) tinha proteinúria na faixa nefrótica no momento do diagnóstico. Os distúrbios subjacentes mais frequentes foram a febre familiar do Mediterrâneo (FFM, 21,2%) e a artrite reumatoide (10,6%) no grupo de desfecho bom e a malignidade (20%) no grupo de desfecho ruim. Somente a pressão arterial diastólica no grupo de desfecho bom e o nível de fósforo no grupo de desfecho ruim foram mais elevados. Os níveis séricos de creatinina aumentaram após o tratamento em ambos os grupos, enquanto a proteinúria diminuiu no grupo de desfecho bom. O aumento na creatinina sérica e a diminuição na TFGe do grupo de desfecho ruim foram mais significativos no grupo de desfecho bom. No momento do diagnóstico, 18,5% e 27,2% de todos os pacientes tinham doença renal crônica avançada (estágios 4 e 5, respectivamente). A duração média da sobrevida renal foi de 65 ± 3,54 meses. Entre todos os pacientes, 27,1% iniciaram tratamento de diálise durante o período de seguimento e 7,4% de todos os pacientes foram submetidos a transplante renal. Níveis elevados de pressão arterial sistólica [taxas de risco (HR) 1,03, intervalo de confiança (IC) de 95%: 1 a 1,06, $p = 0,036$], creatinina sérica (HR 1,25, IC 95%: 1,07 a 1,46, $p = 0,006$) e excreção urinária de proteínas (HR 1,08, IC 95%: 1,01 a 1,16, $p = 0,027$) foram preditores de doença renal terminal. A mediana da sobrevida de pacientes com comprometimento de órgãos foi de 50,3 ± 16 meses.

Conclusão: O presente estudo indicou que a FFM constituiu uma grande proporção de casos e crescente quantidade de pacientes com amiloidose AA idiopática. Adicionalmente, observou-se que a sobrevida do paciente não foi afetada pelas diferentes causas etiológicas na amiloidose AA.

Introduction

The term “amyloidosis” represents a heterogeneous group of diseases caused by the extracellular tissue deposition of low molecular weight subunits of a variety of proteins in the form of insoluble fibers.[1] The main types of systemic amyloidosis are primary light-chain (AL) amyloidosis, amyloid A (AA) amyloidosis, familial amyloidosis, hereditary (associated with an autosomal dominant genetic mutation) or senile (non-mutated) transthyretin amyloidosis (ATTR) and β2-microglobulin-related amyloidosis in patients with end-stage renal disease. The global incidence of amyloidosis is estimated at five to nine cases per million patient-years.[2] AA amyloidosis is also referred to as secondary or reactive amyloidosis, and amyloid deposits occur due to the long-term and sustained supersaturated state of serum amyloid A (SAA) protein, an apolipoprotein of high-density lipoproteins that serves as an acute phase reactant synthesized in the liver, as a consequence of long-standing inflammatory disease.[3] The inflammatory stimuli in AA amyloidosis associate with chronic inflammatory arthritis (rheumatoid arthritis, juvenile chronic polyarthritis, ankylosing spondylitis), inflammatory bowel disease, chronic infections, heredofamilial periodic fever syndromes such as familial Mediterranean fever (FMF), neoplasms, Castleman’s disease and idiopathic causes.[2,4,5] AA amyloidosis is frequent in developing countries and some European regions, and AL amyloidosis is prevalent in developed countries.[2,6]

Kidney involvement is a common manifestation in most types of systemic amyloidosis. Cardiac and neuropathic involvement may be seen rarely. However, kidney shows

variable involvement in patients with AA amyloidosis. The overall renal biopsy incidence of amyloidosis ranges from 1.3% to 4%.[1,7–9] Patients typically present with asymptomatic proteinuria, nephrotic syndrome, progressive renal decline or end-stage renal disease.[10] But, in patients who have amyloid deposition limited in blood vessels or kidney tubules, renal failure may be observed with lower amounts of protein leakage or without proteinuria.[11] The natural history of AA amyloidosis is typically progressive and lead to organ failure and death, especially, in patients with active underlying inflammatory diseases. There are several studies on survival and renal outcomes of patients with AA amyloidosis.[12–14] In this study, we aimed to investigate the patients diagnosed with AA amyloidosis with renal biopsies and analyzed clinical findings, renal survival and mortality.

Patients and methods

In this retrospective observational study, we reviewed the results of renal biopsies of 531 patients who were admitted to our department between January 1st, 2006 and December 31st, 2014. The study included 81 patients who had the diagnosis of AA amyloidosis. The patients were divided into two groups as those with good and poor outcomes according to survival results. We excluded patients with other forms of amyloidosis and those with a presumptive clinical diagnosis (lacking histological confirmation) from analysis. The study was carried out in accordance with the principles of good clinical practice guidelines and the declaration of Helsinki.

Data on detailed history, clinical features (age, gender, weight, height, blood pressure, organ involvement, indication of biopsy, biopsy reports, underlying disease and cause of death) and laboratory results [complete blood count, erythrocyte sedimentation rate (ESR), creatinine, electrolytes, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, triglyceride, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, C-reactive protein (CRP), SAA, intact parathyroid hormone, estimated glomerular filtration rate (eGFR) and 24 h urinary protein excretion (UPE)] at diagnosis were obtained from the medical records. In addition, serum creatinine, albumin, eGFR and 24 h UPE values at the end of follow-up were obtained. Follow-up period included the duration from diagnosis to the last clinical control or to death of the patient.

Nephrotic proteinuria was defined as 24 h UPE $\geq$3 g/day. Amyloid cardiomyopathy was diagnosed when typical features on echocardiography occurred in the absence of other potential causes of left ventricular hypertrophy. The diagnosis of FMF was clinically based and supported by molecular genetic testing (mutations in the gene Mediterranean Fever 5 (MEFV)).[15] We calculated eGFR using with the modification of diet in renal disease formula [GFR = 186 × Pcr (plasma creatinine) − 1.154 × age − 0.203 × 1.212 (if black) × 0.742 (if female)]. Stage of chronic kidney disease was classified according to kidney disease outcomes quality initiative and national kidney foundation (K/DOQI-NKF) guidelines.[16] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters [weight/height^2 (kg/m^2)].

Renal biopsy

All biopsy samples with certain specific diagnoses were included. Light and immunofluorescence (IF) microscopies were performed in all patients. Light microscopic examinations of sections were stained with hematoxylin and eosin, Masson's trichrome, periodic acid Schiff, periodic acid silver methenamine and Congo red. Homogenous amyloid deposits stained positive with Congo red and immunocytochemical AA amyloid stain, and was sensitive to treatment with potassium permanganate that was compatible with secondary amyloidosis. IF microscopy was used for identification of immunoglobulin G (IgG), IgM, IgA, complement 3 (C3), C4 and C1q staining.

Treatment

Most of the patients were treated with colchicine (65.4%, if required, adjusting according to eGFR) and applied a supportive or a specific therapy according to the underlying inflammatory causes and presence of nephrotic syndrome and/or renal insufficiency. Forty eight percent of all patients received angiotensin receptor blockers or angiotensin converting enzyme inhibitors in order to reduce proteinuria.[17] When patients with AA amyloidosis progress to end-stage renal disease, they were given renal replacement therapy (hemodialysis or kidney transplantation).

Statistical analysis

Continuous variables were expressed with median (minimum–maximum) values and categorical variables with frequency and corresponding percentage values. Wilcoxon signed rank test was used for group comparisons. Mann–Whitney, Fisher's exact and Fisher Freeman Halton tests were used between group comparisons. Percentage changes of numerical variables in groups were calculated with the formula: [(second value − first value)/first value] × 100. Life expectancy was calculated by Kaplan–Meier method, Logrank test was used for comparing survival distributions between groups. To determine the prognostic factors that affect overall survival time Cox proportional hazard regression analysis with backward selection procedure was performed after Kaplan–Meier analysis. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). The data was statistically processed by IBM SPSS version 22 software (IBM Acquires SPSS Inc., Somers, NY, USA). In all statistical analysis, $p < 0.05$ was accepted as statistically significant.

Results

AA amyloidosis was found in 15.2% of all patients who underwent renal biopsy in an approximately 10-year period. Biopsy indications for the patients during the initial diagnosis were proteinuria (in nephritic or nephrotic ranges) or renal dysfunction (serum creatinine > 1.5 mg/dL). The ratios of patients with nephrotic range proteinuria ($n = 37$, 56.1% vs. $n = 8$, 53.3%, $p = 0.848$), nephritic range proteinuria ($n = 23$, 34.8% vs. $n = 6$, 40%, $p = 0.763$) and renal dysfunction ($n = 6$, 9.1% vs. $n = 1$, 6.7%,

Table 1 – Characteristics of the patients in the good and poor outcome groups.

Variables	Total ($n=81$)	Good outcome group ($n=66$)	Poor outcome group ($n=15$)	p value
Age (n)	50 (19–83)	50 (19–81)	50 (22–83)	0.894
Gender (male/female) (n)	51/30	40/26	11/4	0.357
Systolic BP (mmHg)	120 (50–180)	120 (50–180)	100 (70–150)	0.189
Diastolic BP (mmHg)	70 (30–110)	77.5 (30–110)	60 (50–80)	0.033
BMI (kg/m^2)	23.44 (15.6–40.1)	23.55 (16.01–35.16)	22.84 (15.6–40.14)	0.484
Hemoglobin (g/dL)	10.9 (6.8–15.8)	10.9 (7.3–15.1)	9.9 (6.76–15.8)	0.670
Sodium (mEq/L)	137 (118–145)	137 (120–145)	136 (118–142)	0.316
Potassium (mEq/L)	4.2 (2.7–5.9)	4.2 (3–5.9)	3.9 (2.7–5.9)	0.394
Calcium (mg/dL)	8.1 (5.7–10.4)	8.1 (7–10.4)	8.2 (5.7–9.3)	0.567
Phosphorus (mg/dL)	4 (2.1–8.2)	3.8 (2.1–8.2)	4.6 (3.2–6.9)	0.025
Cholesterol (mg/dL)	187 (94–569)	181.5 (94–569)	191 (120–569)	0.132
Triglyceride (mg/dL)	142 (45–590)	142.5 (45–590)	145 (89–543)	0.388
AST (IU/L)	18 (8–345)	18 (8–94)	18 (11–345)	0.701
ALT (IU/L)	27 (5–153)	17 (5–100)	16 (6–153)	0.913
PTH (pg/dL)	114 (11.3–654)	109.5 (20–654)	128 (11.3–495)	0.559
CRP (mg/dL)	1.4 (0.3–26.3)	1.3 (0.3–26.3)	1.9 (0.3–20.3)	0.253
ESR (mm/h)	39 (2–120)	35 (2–120)	44 (2–94)	0.293
SAA (mg/L)	27.6 (2.5–412)	27.3 (2.8–412)	34.8 (2.5–278)	0.500

BP, blood pressure; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PTH, parathyroid hormone; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A.

Table 2 – The comparison of changes in renal functions in both groups.

Variables	Good outcome group ($n=66$)			Poor outcome group ($n=15$)		
	Baseline	Post-treatment	p value	Baseline	Post-treatment	p value
UPE (g/day)	4.3 (0.2–28)	2.87 (0–31.0)	0.004	3.88 (1.6–24)	3.12 (1.5–21.5)	0.394
Albumin (g/dL)	2.55 (0.9–4.7)	2.8 (0.9–4.5)	0.119	2.7 (0.5–5)	2.5 (0.4–3.5)	0.135
Creatinine (mg/dL)	1.34 (0.5–8.6)	2.1 (0.5–8.8)	<0.001	1.25 (0.4–3)	3.5 (0.8–8.9)	0.002
eGFR (mL/min/m^2)	57 (7.1–160)	33 (5.2–146)	<0.001	63.9 (22–212)	17 (5–108.2)	0.002

UPE, urine protein excretion; eGFR, estimated glomerular filtration rate.

$p=0.707$) in the good and poor outcome groups did not differ, respectively. The demographic and laboratory characteristics of both groups were similar. Diastolic blood pressure in the good outcome group and phosphorus level in the poor outcome group was higher than those of the other group (Table 1).

The underlying causes of AA amyloidosis in the good outcome group were FMF ($n=14$, 21.2%), rheumatoid arthritis ($n=7$, 10.6%), pulmonary tuberculosis ($n=5$, 7.6%), bronchiectasia ($n=3$, 4.5%), psoriatic arthritis ($n=3$, 4.5%), osteomyelitis ($n=2$, 3%), ankylosing spondylitis ($n=2$, 3%), Behcet's disease ($n=2$, 3%) and Crohn's disease ($n=2$, 3%). In the poor outcome group, the causes were FMF in 2 patients (13.3%), rheumatoid arthritis in 1 patient (6.7%), bronchiectasia in 1 patient (6.7%), gluten enteropathy in 1 patient (6.7%) and malignancy in 3 patients (20%, bladder, lymphoma and lung squamous cell carcinoma). The distributions of underlying causes in both groups were comparable ($p=0.058$). We could not detect any inflammatory disease in 26 (39.4%) patients in the good outcome group and 7 (46.7%) patients in the poor outcome group ($p=0.605$).

The distribution of stages of chronic kidney disease according to eGFR values in the good and poor outcome groups were as follows: (Stage 1: $n=12$, 18.2% vs. $n=3$, 20%; Stage 2: $n=13$, 19.7% vs. $n=1$, 6.7%; Stage 3: $n=12$, 18.2% vs. $n=3$, 20%; Stage 4: $n=15$, 22.7% vs. $n=7$, 46.7% and Stage 5: $n=14$, 21.2% vs. $n=1$, 6.7%, respectively, $p=0.278$). There was no significant difference in baseline serum creatinine, albumin, UPE and eGFR values between both groups. When compared to the baseline values, serum creatinine levels increased and eGFR values decreased after treatment in both groups ($p<0.01$). UPE levels after treatment in the good outcome group decreased ($p=0.004$), while serum albumin levels did not significantly change in both groups (Table 2). The percentage changes in median serum albumin (0% vs. −7.4%, $p=0.055$) and UPE (−14.7% vs. −10.4%, $p=0.511$) levels of the good and poor outcome groups were comparable. Increase in serum creatinine (58.6% vs. 15%, $p=0.042$) and decrease in eGFR (−40.6% vs. −13.9%, $p=0.050$) of the poor outcome group were significant when compared to the good outcome group. There was no significant difference in ratios of mesangial proliferation, tubular, interstitial, arterial, arteriolar involvements, fibrillary spindle, immunoglobulin and complement depositions between groups according to renal biopsy findings (Table 3).

Dialysis

Fifty-three (65.4%) of all patients received medical therapy [44 patients (66.6%) in the good outcome group and 9 patients (60%) in the poor outcome group]. Twenty-two patients (27.1%) started to hemodialysis [17 patients (25.7%) in the good

Table 3 – The comparison of histopathological findings in both groups according to renal biopsy.

Variables, *n* (%)	Total (*n* = 81)	Good outcome group (*n* = 66)	Poor outcome group (*n* = 15)	*p* value
Tubules	64 (79)	51 (77.3)	13 (86.7)	0.726
Mesangial proliferation	12 (14.8)	12 (18.2)	0	0.110
Interstitium	30 (37)	25 (37.9)	5 (33.3)	0.742
Arterial	10 (12.3)	9 (13.6)	1 (6.7)	0.679
Arteriolar	69 (85.2)	55 (83.3)	14 (93.3)	0.449
Arterial and arteriolar	70 (86.4)	56 (84.8)	14 (93.3)	0.331
Fibrillar spindle (Congo red)	72 (88.9)	57 (86.4)	15 (100)	0.198
IgG	8 (9.9)	7 (10.6)	1 (6.7)	1.000
IgM	11 (13.6)	9 (13.6)	2 (13.3)	1.000
IgA	5 (6.2)	4 (6.1)	1 (6.7)	1.000
C3c	9 (11.1)	6 (9.1)	3 (20)	0.356
C1q	3 (3.7)	2 (3)	1 (6.7)	0.464
Periodic acid schiff	16 (19.8)	13 (19.7)	3 (20)	1.000
Masson Trichrome	17 (21)	13 (19.7)	4 (26.7)	0.506
Potassium permanganate	47 (58)	37 (56.1)	10 (66.7)	0.567

Ig, immunoglobulin; C, complement.

outcome group and 5 patients (33.3%) in the poor outcome group], and 6 patients (7.4%) underwent kidney transplantation [5 patients (7.6%) in the good outcome group and 1 patient (6.6%) in the poor outcome group]. Distribution of treatments was similar in both groups ($p = 0.386$). Median renal survival of the patients with or without end-stage renal disease was comparable (68.9 ± 7.9 vs. 60.3 ± 5.1 month, respectively, $p = 0.976$). In one of the amyloidosis patient with kidney transplantation, severe hypoalbuminemia and massive proteinuria via native kidney continued after transplantation despite albumin replacements. After nephrectomy of native kidney, albumin levels increased to normal ranges. There was no significant difference in median renal survival between the good and poor outcome groups ($p = 0.976$) (Fig. 1). Cox regression analysis indicated that higher levels of systolic blood pressure (HR 1.03, 95% CI 1–1.06, $p = 0.036$), serum creatinine (HR 1.25, 95% CI 1.07–1.46, $p = 0.006$) and UPE (HR 1.08, 95% CI 1.01–1.16, $p = 0.027$) at the diagnosis were predictors of end-stage renal disease.

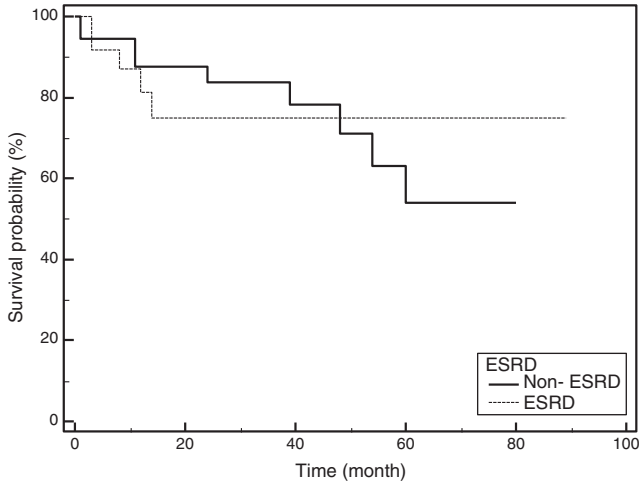

Fig. 1 – Comparison of renal survival in the good and poor outcomes groups ($p = 0.976$).

Survival

When death ratios according to different etiological causes were considered, 2 of 16 FMF (12.5%) patients died [vs. 13 patients (20%) in 65 non-FMF patients, $p = 0.489$], 7 of 33 (21.2%) patients with idiopathic causes died [vs. 8 patients (16.7%) in 48 patients with non-idiopathic causes, $p = 0.605$], 1 of 11 infectious (9.1%) patients died [vs. 14 patients (20%) in 70 non-infectious patients, $p = 0.387$] and 1 of 17 (5.8%) inflammatory diseases patients died [vs. 14 patients (21.9%) in 64 patients with non-idiopathic causes, $p = 0.131$]. There was also no significant difference between median survival times of groups with different etiological causes (Table 4).

The median survival (50.3 ± 16.0 months) in patients with organ involvement was not different from the patients without organ involvement (64.8 ± 5.41 months) ($p = 0.790$) (Fig. 2). There was a significant difference in median survival between patients with and without tubular involvement (57.6 ± 6.4 vs. 67.7 ± 4.2 months, respectively, $p = 0.038$) at the diagnosis

Table 4 – Median survival times in renal functions of patients with AA amyloidosis according to etiological causes.

Causes of AA amyloidosis	Survival time (months)	*p* value
Infectious		
Yes (*n* = 11)	44.7 ± 4.92	0.718
No (*n* = 70)	64.8 ± 5.36	
FMF		
Yes (*n* = 16)	60.7 ± 7.78	0.338
No (*n* = 65)	62.5 ± 5.97	
Inflammatory diseases		
Yes (*n* = 17)	81.7 ± 6.81	0.091
No (*n* = 64)	56.1 ± 5.14	
Unknown (idiopathic)		
Yes (*n* = 33)	53.9 ± 7.93	0.313
No (*n* = 48)	69.2 ± 5.99	

FMF, familial Mediterranean fever.

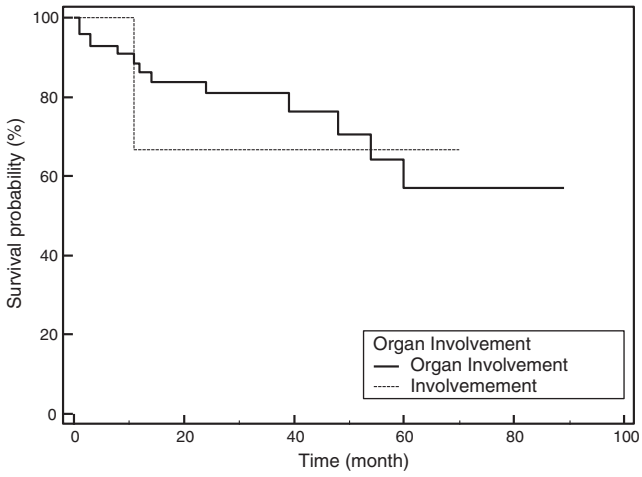

Fig. 2 – Comparison of survival in the good and poor outcomes groups according to presence of organ involvement ($p = 0.790$).

(Fig. 3). Cox regression analysis did not reveal a significant model on mortality.

Cause of death

At the end of follow-up period, causes of death were sepsis or septic shock ($n = 5$, 33.3%), heart failure ($n = 4$, 26.6%), cerebrovascular disease ($n = 3$, 20%) and multiple organ failure ($n = 3$, 20%). Six patients (7.4%) had organomegaly or organ involvement findings in our cohort (4 cardiac, 1 cerebrovascular and 1 liver involvements).

Discussion

Renal involvement is a common complication in systemic amyloidosis. AA amyloidosis is the second most common form of systemic amyloidosis. In our study, AA amyloidosis was found in 81 patients (15.2%) from an overall number of 531 renal biopsies. When seven patients who got the diagnosis of AL amyloidosis in this period were also included, the ratio rose to 16.5%.[18] The data on 4004 native kidney biopsies performed in the Czech Republic between 1994 and 2000 years showed that renal amyloidosis was 9.9% of secondary glomerulonephritis.[19] Renal biopsy proven amyloidosis constituted 0.68% (18 AL and 22 non-AL cases), 2.1% [407 AL/fragments of Ig heavy chains and light chains (AHL)/fragments of heavy chains only (AH) and 33 AA cases], 2.5% (32 AA and 8 AL cases) and 4.65% (46 AA cases) of the total cases of native renal biopsies performed in different centers from Taiwan, USA, Egypt and Czech Republic, respectively.[8,14,20,21] The Italian Registry of Renal Biopsies reported a frequency of 2.5% of renal amyloidosis among 14,777 renal biopsies in a 7-year period.[22] There are limited data on the incidence of amyloidosis probably because of its rarity and heterogeneity. A recent study investigated the incidence of amyloidosis based on nation wide hospitalization in Sweden.[23] For years 2001–2008, the incidence of non-hereditary amyloidosis in 949 patients was 8.29 per million person years. Unspecified amyloidosis was the largest group (535 patients, incidence: 4.69/million), followed by secondary systemic amyloidosis (136 patients, 1.18/million). Another center in the eastern region of Turkey assessed 128 biopsies from various sites of 111 patients with biopsy proven amyloidosis.[24] There were 101 (90.9%) patients diagnosed as having AA amyloidosis. Among 69 renal biopsies, 65 patients had AA amyloidosis and 4 patients had mixed amyloidosis (AL + AA types in 2 and AA + ATTR types in 2). The relatively higher rate of amyloidosis in our biopsy series can be explained by the fact that our hospital is the only reference center in the Southern Marmara region of Turkey. Furthermore, amyloidosis patients with or without proteinuria may be referred to other clinics such as rheumatology and hematology, and biopsies can be performed from different locations other than kidney and treated. These patients are referred to our department after severe renal failure developed.

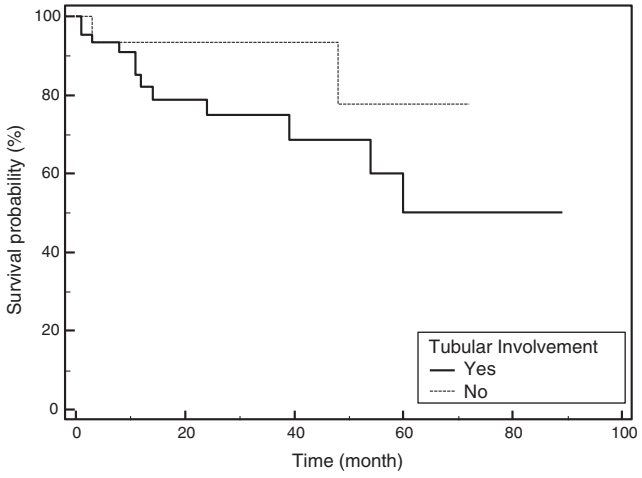

Fig. 3 – Comparison of survival in the good and poor outcomes groups according to presence of tubular involvement ($p = 0.038$).

In developed countries, rheumatoid arthritis is the most common cause of AA amyloidosis with renal involvement, while in developing countries patients with untreated FMF and chronic suppurative infections constitute a large proportion of AA amyloidosis cases.[25–27] In various studies, FMF appears to be the leading cause of AA amyloidosis in Turkey, followed by tuberculosis.[12,26,28] Among 287 cases of renal amyloidosis in a study from 11 nephrology centers in Turkey, 64% had FMF as the leading cause, followed by tuberculosis 10%, bronchiectasia and chronic obstructive lung disease 6%, rheumatoid arthritis 4%, spondylarthropathy 3%, chronic osteomyelitis 2%, miscellaneous 4% and unknown 7%.[28] In our study, the most frequent underlying cause of AA amyloidosis was FMF (19.7%), followed by chronic rheumatic diseases (18.5%), chronic infections (13.5%) and malignancy (3.7%), and this observation was consistent with previously reported findings from our country.[26,28] There was also no significant difference in the distribution of underlying causes between the good and poor outcome groups. FMF is the main cause of AA amyloidosis among individuals with various ethnic origins such as Jews, Arabs, Armenians and Turks in Mediterranean-Middle Eastern regions.[29] The estimated prevalence of FMF in Turkey is 0.1%. However, it is thought that the prevalence may be higher since

many patients are undiagnosed. Recently, we determined the frequency of MEFV mutation in 116 adults with FMF cases.[30] Fifteen patients (12.7%) had proteinuria, 10 patients (8.6%) had chronic kidney disease and 7 (6%) had amyloidosis. We found significantly higher frequency of G allele of G138G and A allele of A165A polymorphisms. However, we could not find a significant association between these polymorphisms and clinical findings including chronic kidney disease, proteinuria and amyloidosis in these patients.

In a large study no cause could be detected in 23 (6.1%) of 374 patients with AA amyloidosis.[31] At the time of diagnosis and follow-up, we could not detect any inflammatory disease in 33 (40.7%) patients. Similarly, the cause of AA amyloidosis at diagnosis remains obscure in 29.2% and 32.4% of cases in two studies, despite a detailed search for the underlying inflammatory or infectious causes.[32,33] A retrospective study including patients with AA amyloidosis (95% having renal involvement) at Mount Sinai during the period of 1997–2012 revealed consistently elevated interleukin-6 levels in most of idiopathic patients (21% of 43 cases) and E148Q pyrin gene mutation (in 3 of 9 tested).[34] The possibility that some of the idiopathic cases in our cohort may be FMF should not be ignored due to the widespread occurrence of FMF in Turkey, retrospective design of our study and conducting genetic evaluation of FMF after 2011 in our center. Therefore, we prefer to start colchicine treatment in patients with idiopathic AA amyloidosis, except the ones with advanced chronic kidney disease.

Tsai et al.[20] reported 80% of patients with amyloidosis had nephrotic syndrome (mean UPE 6.9 ± 4.7 g/day) and 40% of them had low GFR values (<50 mL/min/m^2). In another study from Spain, 69.5% of patients with amyloidosis had nephrotic syndrome (UPE 6 g/day) and GFR values were lower than 60 mL/min/m^2 in 70% of AA amyloidosis group.[35] An Italian collaborative study on survival and renal outcome described that 43% of patients with AA amyloidosis had stage 5 CKD.[36] Amyloidosis sometimes can be diagnosed accidentally. Previously, we presented an ureamic patient who got a diagnosis of AA amyloidosis after unilateral nephrectomy because of life-threatening spontaneous perirenal hematoma.[37] In the present study, age, gender distribution, systolic blood pressure, BMI, serum albumin, creatinine, UPE (proteinuria in nephrotic ranges), eGFR (stages of chronic kidney disease), histopathological and IF findings and need for dialysis treatment in the good and poor outcome groups were comparable at the diagnosis. Only diastolic blood pressure in the good outcome group and phosphorus level in the poor outcome group was higher than the other group. Serum creatinine levels increased and eGFR values decreased after treatment in both groups. However, the changes in serum creatinine and eGFR of the poor outcome group were more significant than the good outcome group. There was nephrotic syndrome in 55.6% of all patients. UPE levels after treatment in the good outcome group decreased. The eGFR values were under 60 mL/min/m^2 in 87.5% of the good outcome group and 73.3% of the poor outcome group. Renal involvement occurs early in the course of AA amyloidosis. A lower renal survival with a higher number of patients who progressed to end-stage renal disease was observed in patients with renal AA amyloidosis.[36] In our cohort, the ratio of patients receiving dialysis treatment was 27.6%, and median renal survival in the good and poor outcome groups did not differ. We determined that higher levels of systolic blood pressure, serum creatinine and UPE were independent risk factors for end-stage renal disease. Other studies found that age, heart involvement, serum creatinine and albumin levels were predictors of end-stage renal disease.[36,38]

AA amyloidosis is a multisystem, progressive and fatal disease. Complications of end-stage renal disease are the main causes of death and median survival after diagnosis varies between 4 and 10 years.[13,39] In the present study, median overall survival time was 50.3 ± 16.0 months in patients with organ involvement and, median renal survival time was 65 ± 3.54 months. The previously published series related renal AA amyloidosis is summarized in Table 5. We did not find a significant difference in death ratios and survival time of patients with FMF, chronic inflammatory disease, chronic infection or unknown disorder when we considered different etiological causes. Also presence of organ involvement did not affect survival. There was only a significant difference in the median survival between patients with and without tubular involvement. Among 474 patients with renal amyloidosis, vascular involvement was more frequent and extensive in AL/AH/AHL and AA compared with other types. The degree of tubular atrophy and interstitial fibrosis in AA was higher than AL/AH/AHL.[8] Several studies reported that older age, male gender, tuberculosis etiology, advanced renal disease, lower levels of BMI, eGFR, calcium and albumin, and higher levels of creatinine, UPE, phosphorus and intact parathyroid hormone were associated with a worse prognosis.[12,38,40] Additionally, heart involvement, higher serum creatinine, lower albumin, dialysis requirement and short time to dialysis were predictors of mortality.[12,38] Organ involvement (7.4%) was low in our cohort. However, amyloid-related heart involvement at the diagnosis is one of the unfavorable predictive factors in AA amyloidosis patients with rheumatic diseases.[41] We did not determine any independent risk factor for mortality. These results can explained by the relatively small number of patients who had organ involvement or died.

ESR, CRP and SAA levels were high in most of our patients, but there was no statistically significant difference between the good and poor outcome groups. CRP and SAA are acute phase reactants which are synthesized via pro-inflammatory cytokines.[3] Mean plasma concentration of SAA is about 3 mg/L in healthy individuals, but its concentration can increase to 2000 mg/L in inflammatory processes. The level of SAA is a powerful predictor of both survival and renal outcome in patients with AA amyloidosis.[10] Moreover, SAA is associated with response to treatment in the course of AA amyloidosis. The serial measurement of SAA levels can be useful. It has been observed that SAA correlated with amyloid burden, renal prognosis and mortality in the follow-up of 374 patients with AA amyloidosis.[31] A SAA level under 4 or 10 mg/L is associated with a favorable outcome.[31,42] Amyloid load increased and organ function deteriorated in most patients in whom SAA was persistently above 50 mg/L.[42]

The most important limitations of our study were the analysis of retrospective data and inclusion of relatively small number of patients with different etiologies. As a result, incidence of renal amyloidosis related to FMF is increasing in

Table 5 – Patient number, profile and the timing, distribution of underlying diseases, renal outcomes and survival in some studies related AA amyloidosis all over the world.

Country[a]	Time interval	Amyloid type	M/F	Age (y)	Underlying causes	SCr (mg/dL)	UPE (g/day)	ESRD (dialysis)	Outcomes and survival
Turkey[12]	NA	73 AA	49/24	41.8 ± 15.8	FMF 26%, TB 21.9%, COPD 10.9%, rheumatic diseases 6.8%, others 5.4%, unknown 28.7%	4.65 ± 4.89	8.04 ± 6.09	61.6%	30 (41%) died 35.9 ± 6.1 mo
Egypt[14]	2003–2009	32 AA	20/12	36.5 ± 10.3	FMF 37.5%, TB 25%, osteomyelitis 12.5%, bronchiectasia 12.5%, RA 9.3%, others 3.1%	1.9 ± 0.8	5.46 ± 3.26	21.8%	1 (3.1%) died
Turkey[26]	NA	59 AA	45/14	33 ± 13 (16–66)	FMF 30.5%, TB 20.3%, osteomyelitis 13.5%, bronchiectasia 15.25%, rheumatic diseases 6.4%, others 1.6%, unknown 11.8%	CCr; 51.0 ± 40.6 mL/min	5.18 ± 2.6 (0.2–24.5)	20.3%	9 (15.2%) died
Spain[27]	2000–2010	30 AA	14/16	62 ± 14	RA 30%, AS 13.3%, chronic infections 10%, tumors 6.6%, IBD 6.6%	2.3 ± 2.0	3.16 ± 2.73	20% (30 AA + 24 AL)	31 (57.4%) died (30 AA + 24 AL)
England[31]	1990–2005	374 AA	210/164	50 (9–87)	Rheumatic diseases 59.8%, chronic infections 14.9%, FMF 5.3%, others 10.9%, unknown 6.1%	1.78 (0.37–13.9)	3.9 (0–26)	41.4%	163 (44%) died 133 (100–153) mo
Italy[36]	1995–2000	86 AA	36/50	62 (19–86)	NA	1.6 (0.5–12.4)	5.0 (0.5–29.8)	14%	34 (39.5%) died 30 (1–99) mo
Turkey[38]	2001–2013	121 AA	87/34	42.6 ± 14.4	FMF 37.2%, TB %24.8, unknown 19.8%, rheumatic diseases 8.2%, COPD 6.6%, others 3.3%	2.3 ± 2.1	6.7 ± 5.3	56.2%	50 (41.3%) 88.7 ± 7.1 mo
Japan[41]	1983–2001	42 AA	7/35	51.3 ± 19.5 (M) 55.3 ± 19.8 (F)	Rheumatic diseases 100% (RA 36)	NA	NA	NA	27 (64.2%) died
Actual	2006–2014	81 AA	51/30	50 (19–83)	FMF 19.7%, rheumatic diseases 18.5% (RA 8), chronic infections 13.5% (TB 5), others 4.9%, unknown 40.7%	1.28 (0.4–8.6)	4.24 (0.2–28)	27.1%	15 (18.5%) 50.3 ± 16.0 mo (organ)

M, male; F, female; SCr, serum creatinine; UPE, urinary protein excretion; ESRD, end-stage renal disease; CCr, creatinine clearance; RA, rheumatoid arthritis; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; KT, kidney transplantation; FMF, familial Mediterranean fever; TB, tuberculosis; COPD, chronic obstructive pulmonary diseases; NA, not available.

[a] Reference number. Numeric values were given as *n*, mean (±SD) or median (ranges).

our region. Surprisingly, a remarkable increase is seen in the number of AA amyloidosis cases in whom underlying cause is not determined. Therefore, amyloidosis should be considered in the differential diagnosis of patients presenting with nephrotic syndrome or unexplained uremia, and renal biopsy should be performed. Genetic testing for the diagnosis of FMF should be used more often. Diagnosis and treatment of chronic inflammatory diseases are crucial for reducing the development of AA amyloidosis in the next years and improving survival.

Conflicts of interest

The authors declare no conflicts of interest.

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