Amyloid A Amyloidosis After Renal Transplantation: An Important Cause of Mortality

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Background. There are limited data on the outcome of transplant recipients with familial Mediterranean fever (FMF)-associated AA amyloidosis. The aim of the present study is to evaluate demographic, clinical, laboratory, and prognostic characteristics and outcome measures of these patients. **Methods.** Eighty-one renal transplant recipients with FMF-associated AA amyloidosis (group 1) and propensity score–matched transplant recipients (group 2, n = 81) with nonamyloidosis etiologies were evaluated in this retrospective, multicenter study. Recurrence of AA amyloidosis was diagnosed in 21 patients (group 1a), and their features were compared with 21 propensity score–matched recipients with FMF amyloidosis with no laboratory signs of recurrence (group 1b). **Results.** The risk of overall allograft loss was higher in group 1 compared with group 2 (25 [30.9%] versus 12 [14.8%]; $P = 0.015$ [hazard ratio, 2.083; 95% confidence interval, 1.126-3.856]). Patients in group 1 were characterized by an increased risk of mortality compared with group 2 (11 [13.6%] versus 0%; $P = 0.001$ [hazard ratio, 1.136; 95% confidence interval, 1.058-1.207]). Kaplan-Meier analysis revealed that 5- and 10-year patient survival rates in group 1 (92.5% and 70.4%) were significantly lower than in group 2 (100% and 100%; $P = 0.026$ and $P = 0.023$, respectively). Although not reaching significance, overall, 5- and 10-year graft survival rates (57.1%, 94.7%, and 53.8%, respectively) in group 1a were worse than in group 1b (76.2%, 95%, and 77.8%, respectively; $P = 0.19$, $P = 0.95$, and $P = 0.27$, respectively). **Conclusions.** AA amyloidosis is associated with higher risk of mortality after kidney transplantation. Inflammatory indicators should be monitored closely, and persistent high levels of acute-phase reactants should raise concerns about amyloid recurrence in allograft.

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INTRODUCTION

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent attacks of fever and polyserositis as manifested by abdominal, chest, or joint pain.[1] It is mostly prevalent in Israeli, Turks, North Africans, Arabs, Armenians, and populations surrounding the Mediterranean Sea. However, in recent years, ever more FMF cases are being reported from Europe, United States, and even from Japan very probably due to migration or marriages among different ethnicities.[2] Acute attacks of FMF are usually accompanied by leukocytosis and increased levels of acute-phase reactants, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A protein (SAA). The most severe complication in these patients is secondary amyloid A (AA) amyloidosis of the kidneys, which can lead to end-stage kidney disease (ESKD).[1,3,4] Amyloid deposition can also occur in several other organs, which include, but are not limited to, liver, gastrointestinal tract, heart, and thyroid. Extensive involvement in all these organs may lead to organ dysfunction and may result in mortality.

Renal transplantation is the treatment of choice in ESKD; however, for patients with renal amyloidosis, recurrence of amyloid A deposition in the allograft remains a concern. Data about transplant outcomes are quite scarce and inconsistent in the literature; some report similar patient and graft outcomes compared with general transplant

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population,[5,6] while others have underlined unfavorable outcomes.[7-9] Therefore, this study aimed to evaluate clinical and laboratory characteristics of renal transplant recipients with primary disease of FMF-related AA amyloidosis and predictors and effects of recurrence on patient and renal allograft outcomes.

MATERIALS AND METHODS

Patients

This retrospective multicenter analysis was conducted in 4 renal transplantation centers. A total of 162 renal transplant recipients (112 male and 50 female) were included in the study. Primary disease leading to ESKD was FMF-associated renal AA amyloidosis in 81 patients and other diseases in the propensity score–matched 81 control cases. The majority (82%) of transplantations were performed from living donors (Table 1).

FMF diagnosis was based on clinical and laboratory findings and/or genetic mutation (Mediterranean fever gene) analyses. Eighty-one patients with FMF and biopsy-proven AA amyloidosis (group 1) transplanted in the study centers were retrospectively evaluated. Propensity score–matched 81 transplant recipients (group 2) among 915 cases, whose primary renal disease was not amyloidosis, served as controls. Primary kidney diseases of group 2 leading to kidney transplantation were as follows: 13 had chronic glomerulonephritis, 7 immunoglobulin A (IgA) nephropathy or IgA vasculitis, 7 reflux nephropathy, 7 hypertensive nephrosclerosis, 4 chronic pyelonephritis, 3 diabetic nephropathy, 3 postpartum kidney failure, 3 congenital anomalies of kidney and urinary tract other than vesicoureteral reflux, 2 polycystic kidney disease, 2 focal segmental glomerulosclerosis, 2 membranoproliferative glomerulonephritis, 2 Alport syndrome, and 1 lupus nephritis. Underlying renal diseases of 25 patients were unknown; however, lack of any evidence pointing out primary or secondary amyloidosis in these patients helped to exclude amyloidosis (ie, medical history, clinical examination, and laboratory findings). The propensity model was a logistic regression of renal transplant recipient type (recipients with FMF-associated amyloidosis [group 1] versus other nonamyloidosis etiologies [group 2]) including all recipient characteristics as independent variables, and the propensity score was the linear prediction from this model.[10]

Considering its unfavorable effects on the ultimate outcome, FMF patients with cardiac amyloidosis were excluded from our transplant program. To rule out this complication, all transplant candidates with a history of amyloidosis were initially evaluated by echocardiography (performed by an experienced cardiologist). A cardiac magnetic resonance imaging followed this examination if the echocardiography was suggestive or unclear for cardiac amyloidosis. Patients were eliminated from the transplant program if the results were in line with cardiac amyloidosis.

Immunosuppressive Therapy

Induction therapy (ATG Fresenius, 2 mg/kg/d, for 3–7 d) was used in all transplantations from deceased donors. All the patients received intraoperative methylprednisolone bolus injection at a dosage of 500 mg and afterwards were treated by triple maintenance immunosuppressive regimen including a calcineurin inhibitor (CNI) (cyclosporine or tacrolimus), an antiproliferative drug (azathioprine [AZA]

TABLE 1.

Demographic, clinical, and therapeutic features of study patients

	AA amyloidosis (group 1) (n = 81)	Control group (group 2) (n = 81)	*P*
Age (y)	34 ± 12	33 ± 11	0.45
Sex (M/F)	57 (70%)/24 (30%)	55 (68%)/26 (32%)	0.73
BMI (kg/m^2)	22.1 ± 3.7	22.7 ± 4.2	0.78
Donor age (y)	45 ± 14	46 ± 11	0.51
Donor sex (M/F)	34 (42%)/47 (58%)	28 (35%)/53 (65%)	0.33
Donor type (living/deceased)	64 (79%)/17 (21%)	69 (85%)/12 (15%)	0.31
HLA mismatches	2.9 ± 1.4	3.1 ± 1.4	0.22
Follow-up period (IQR) (mo)	90 (60–117)	88 (63–110)	0.98
Initial immunosuppressive treatment, n (%)			
CNI/MMF/PRD	57 (70)	63 (78)	0.14
CNI/AZA/PRD	22 (27)	13 (16)	
mTORi/MMF/PRD	2 (3)	5 (6)	
Maintenance immunosuppressive treatment, n (%)			
CNI/MMF/PRD	45 (56)	59 (73)	
CNI/AZA/PRD	24 (29)	11 (14)	0.07
mTORi/AZA/PRD	5 (6)	6 (7)	
MMF/PRD	7 (9)	5 (6)	
Laboratory characteristics during follow-up			
Mean hsCRP (mg/L)	9 ± 6.6 (1.4–35.8)	1.8 ± 1.3 (0.5–6.9)	<0.001
Mean ESR (mm/h)	24.7 ± 10.5 (7.5–56)	14.1 ± 4.3 (6–24)	<0.001

AA, amyloid A; AZA, azathioprine; BMI, body mass index; CNI, calcineurin inhibitor; ESR, erythrocyte sedimentation rate; F, female; HLA, human leukocyte antigen; hsCRP, high-sensitive *C*-reactive protein; IQR, interquartile range; M, male; MMF, mycophenolate mofetil/sodium; mTORi, mammalian target of rapamycin inhibitor; PRD, prednisone.

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or mycophenolate mofetil/sodium [MMF]), and prednisolone. CNIs were initiated 2 days and antiproliferatives 1 day before in living donor transplantations. Target blood levels of cyclosporine (C0) and tacrolimus after transplantation were 200–300 ng/mL and 8–12 ng/mL for the first 3 months and 50–150 ng/mL and 4–8 ng/mL for subsequent months, respectively. MMF and AZA were administered at a dosage of 2 g/day (1440 mg/d for mycophenolate sodium) and 1.5 mg/kg/day, respectively. On postoperative day 1, patients received methylprednisolone beginning with a dose of 120 mg daily, with a rapid taper and reaching to maintenance dose of 10 mg daily within the first month and 5 mg daily within the first year. Alterations were made in treatment strategies per immunologic risk and posttransplant complications, if necessary. Patients with FMF also continued their treatment including colchicine in dosages of 1.5–2 mg/day after transplantation.

Maintenance immunosuppressive regimen was defined at 3 months after kidney transplantation. If the maintenance treatment was altered during the follow-up after the first 3 months, immunosuppressive treatment regimen at the last follow-up was recorded as maintenance treatment. There were no human leukocyte antigen (HLA) identical transplantations. For some patients, CNIs were decreased or stopped because of the side effects of immunosuppression and infections in the long term.

Follow-up Principles

Patients were followed up at the transplantation clinic at weekly intervals in the beginning; the follow-up intervals were increased to 1 month and 3 months by time. Laboratory data including serum creatinine, albumin, high-sensitive CRP (hsCRP), ESR, serum levels of cyclosporine and tacrolimus, complete blood count, and quantitative proteinuria measurements were retrieved from patients' charts. Fasting serum samples for biochemical studies were obtained between 08:00 AM and 08:30 AM in all cases. Laboratory values, including complete blood cell count and serum levels of creatinine, albumin, and hsCRP, were measured using standard enzymatic procedures. The urinary protein-to-creatinine ratio in the first morning urine specimen was used to estimate quantitative proteinuria. Laboratory parameters measured during an acute infection episode were not included in the analyses.

Allograft biopsy was performed to patients in the case of allograft dysfunction and/or proteinuria ≥1 g/day. Allograft AA amyloidosis recurrence was histologically proven in 21 (26%) patients with new onset proteinuria or persistent unexplained increase in serum creatinine. Characteristics of the patients with amyloidosis recurrence in the allograft (group 1a, n = 21) were compared with 21 propensity score–matched nonrecurrent AA amyloidosis patients for each recipient in group 1a. Propensity score matching was performed among 60 nonrecurrent AA amyloidosis patients, who have no clinical or laboratory signs of recurrence to identify age, sex, donor age, donor sex, HLA mismatch, and follow–up time–matched recipients.

Time to recurrence was described as the months between transplantation and the biopsy of the allograft that revealed amyloid deposition. The follow-up period was considered as the time interval between renal transplantation and the last outpatient visit, kidney failure, or death.

Histopathologic Evaluation

Adequate renal biopsy specimens, which were defined as having 7 or more glomeruli with at least 2 arteries, were evaluated. Three- to 4-micrometer sections were used for all histochemical and immunohistochemical staining. 0.4–0.6 cm unfixed tissue was frozen with liquid nitrogen for immunofluorescence staining (IgG, IgM, IgA, complement component 1q, complement component 3, fibrinogen, and kappa and lambda light chains). Remaining tissues were fixed in Hollande's fixative, embedded in paraffin, and processed routinely for light microscopic evaluation (hematoxylin and eosin, periodic acid-Schiff, methenamine silver-periodic acid, Masson trichrome, Congo red). Banff criteria[11,12] were used when evaluating the specimens by light microscopy. Complement component 4d staining was performed by immunohistochemistry on paraffin-embedded tissue blocks. Linear and circumferential staining in peritubular capillaries were regarded as positive according to the recent Banff scoring system (C4d, >0).[11] Histopathologic diagnosis of renal AA amyloidosis was determined by demonstration of an apple green birefringence under polarized light by Congo red staining and positive immunostaining with specific monoclonal antibodies to SAA.

Study Outcomes

Patient and graft survival rates were the primary outcomes of the study. Graft loss was described as the graft dysfunction, which necessitated dialysis or retransplantation, or death with a functioning graft. Biopsy-confirmed allograft rejection was the secondary outcome. The impact of recipients' and donors' various features (age, sex, donor type, donor age, donor sex, and number of HLA mismatches) on primary and secondary outcomes was also analyzed.

Statistical Analyses

Statistical analyses were performed by using SPSS software for Windows (SPSS version 25.0; IBM Corp., Armonk, NY) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).[13] Data were expressed as mean ± standard deviation when normally distributed or as the median (interquartile range [IQR]) otherwise. Parametric and nonparametric tests were used according to the distribution pattern of the data. Propensity scores were generated using a multivariable logistic regression model based on the baseline recipient sex, donor source (living or deceased), donor sex, number of HLA mismatches, and continuous variables of recipient age, donor age, and follow-up time differences between groups 1 and 2.[14] To obtain the most similar transplant recipient control without amyloidosis for each case with FMF-associated amyloidosis, matching process using the nearest neighboring method in 1:1 ratio was performed.[14] Propensity scores were also generated by multivariable logistic regression model as described above for groups 1a and 1b, and matching process using the nearest neighboring method in 1:1 ratio was performed. Because patients were eliminated from the transplant program if their results were in line with cardiac amyloidosis, cardiac involvement was not integrated in the propensity score.

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Comparisons of continuous variables between the 2 groups were assessed by using the unpaired *t* test or the Mann-Whitney *U* test, where appropriate. The differences in the proportions of different patient groups were compared by the Fisher exact test. Univariate survival comparisons were made by using the log-rank test. Patient and allograft survival were analyzed by the Kaplan-Meier method, and the allograft survival time for each patient was computed from transplantation time to the last follow-up or the primary outcome. Relationships were determined by Pearson correlation coefficient. Variables previously found to affect allograft survival in the univariate analysis were included in the multivariate Cox proportional hazards model. Variables were selected by backward elimination using likelihood ratio tests. All statistical tests were 2-sided, and the level of statistical significance was set at $P < 0.05$.

Istanbul Faculty of Medicine Ethics Committee approved the study and registered with ClinicalTrials.gov (number: NCT02704065).

RESULTS

Baseline Clinical, Histopathologic, and Therapeutic Features

Demographic, clinical, and therapeutic features of study patients are shown in Table 1. The study groups were similar regarding age, sex, body mass index, donor age, donor sex, donor type, number HLA mismatches, and follow-up time (Table 1). The median time on dialysis for all patients was 20 months (IQR 25–75, 6.5–48 mo). Posttransplantation initial immunosuppressive treatment was similar between patients in groups 1 and 2 ($P = 0.14$) (Table 1). About maintenance immunosuppression, although not reaching significance, use of AZA-containing regimens was higher in group 1 compared with group 2 ($P = 0.07$) (Table 1).

Pretransplant donor-specific anti-HLA antibodies were negative in all study group patients before kidney transplantation. During follow-up period, 1 patient in recurrent AA amyloidosis group developed class I donor-specific antibody with 1000–3200 mean fluorescence intensity (MFI), and 2 patients in nonrecurrent AA amyloidosis group developed class II donor-specific antibodies with 1000–8200 MFI and 3000–5000 MFI levels, respectively.

Comparison of Subgroups

In a total of 21 (25.9%) patients (group 1a), AA amyloidosis recurred at the allograft after a median of 79 months (IQR, 59–134 mo). When group 1a was compared with propensity score–matched nonrecurrent AA amyloidosis cohort (group 1b), age, sex, donor type, donor age, donor sex, follow-up time, and HLA mismatches did not differ among the groups (Table 2). The median time on dialysis was 27 months (IQR, 5–57 mo) for group 1a, 18 months (IQR, 8.5–40.5 mo) for group 1b, and 19 months (IQR, 6–55.5 mo) for group 2. Time on dialysis did not differ significantly among all groups ($P = 0.82$).

Mean serum creatinine and level of proteinuria were 1.70 ± 0.7 mg/dL and 2.4 ± 1.5 g/24 h, respectively, at the time of biopsy in group 1a. During the follow-up period, median hsCRP levels in group 1a (12.6 mg/L; IQR, 7.3–18.7) were significantly higher than in group 1b (5.7 mg/L; IQR, 3.8–8.8) ($P = 0.014$). Mean ESR of patients was also significantly higher in group 1a (35.2 ± 11.6 mm/h) compared with group 1b (21.6 ± 7.4 mm/h) ($P < 0.001$) (Table 3). At last follow-up, median daily proteinuria levels were significantly higher and mean serum albumin levels were significantly lower in group 1a (0.89; IQR, 0.59–3.45 g/24 h and 3.6 ± 0.8 g/dL, respectively) compared with group 1b (0.17; IQR, 0–0.19 g/24 h and 4.5 ± 0.4 g/dL, respectively) ($P = 0.003$ and $P = 0.03$, respectively). There were no significant differences about serum creatinine and estimated glomerular filtration rate levels at last follow-up between group 1a and group 1b ($P = 0.16$ and $P = 0.30$) (Table 2).

During the follow-up period, 2 patients in group 1a, 1 patient in group 1b, and 1 patient in group 2 were switched to mammalian target of rapamycin inhibitor–based regimen due to CNI-related side effects (Table 1). Also, immunosuppressive regimens of 3 patients in recurrent AA amyloidosis group (group 1a) were switched from triple therapy to MMF and prednisone treatment. No significant difference was noted in terms of immunosuppressive protocols between group 1a and group 1b (Table 2).

All patients with FMF were on colchicine treatment at the time of transplantation; however, during the posttransplantation follow-up period, 6 (28.6%) patients in group 1a administered anakinra (interleukin 1 receptor antagonist) after recurrence of amyloidosis confirmed by allograft biopsy while none of the patients in group 1b received this treatment ($P = 0.008$).

Study Outcomes

Overall, median follow-up time after transplantation was 90 months (IQR, 63–112 mo). There was no statistically significant difference about biopsy-confirmed acute rejection rates among groups (group 1 [n = 11, 13.6%] and group 2 [n = 19, 23.5%]; $P = 0.11$) (Table 3). When group 1a (recurrent AA amyloidosis) was compared with propensity score–matched nonrecurrent AA amyloidosis cohort (group 1b), there was also no statistically significant difference about biopsy-confirmed acute rejection rates (group 1a [n = 4, 19%] and group 1b [n = 6, 28.6%]; $P = 0.47$) (Table 4).

A total of 37 recipients lost their allografts after a median follow-up time of 64 months (IQR, 6–109). The risk of overall allograft loss was higher in group 1 compared with propensity score–matched counterparts in group 2 (25 [30.9%] versus 12 [14.8%]; $P = 0.015$ [hazard ratio, 2.083; 95% confidence interval, 1.126-3.856]) (Table 2). However, the lower figures for 5-year (83.6% in group 1 versus 92.8% in group 2) and 10-year graft survival rates (48.6% in group 1 versus 58.3% in group 2) did not reach statistical significance in Kaplan-Meier analysis ($P = 0.094$ and $P = 0.434$, respectively) (Figure 1A). The causes of allograft loss in group 1 were as follows: death with a functioning graft (11 [13.5%]), recurrent amyloidosis (5 [6.2%]), chronic antibody-mediated rejection (5 [6.2%]), sepsis (3 [3.7%]), and primary nonfunction (1 [1.2%]). In group 2, chronic antibody-mediated rejection was responsible for graft loss in 7 patients (8.6% patients). Other causes were as follows: recurrent glomerulonephritis and acute rejection in 2 (2.5%) each and BK virus nephropathy in 1 (1.2%) patient. Death-censored 5-year (89.7% in group 1 versus 92.8% in group 2) and 10-year (63% in group 1 versus 58.3% in group 2) allograft survival rates were also similar between groups 1 and 2 ($P = 0.542$ and $P = 0.77$, respectively).

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TABLE 2.

Demographic, clinical, therapeutic, and laboratory features of patients recurrent and nonrecurrent AA amyloidosis patients

	Recurrent AA amyloidosis (group 1a) (n = 21)	Nonrecurrent AA amyloidosis (group 1b) (n = 21)	*P*
Age (y)	29 ± 9	31 ± 11	0.59
Sex (M/F)	57 (70%)/24 (30%)	55 (68%)/26 (32%)	0.73
BMI (kg/m^2)	20.4 ± 3.4	22.1 ± 4.9	0.28
Donor age (y)	39 ± 14	43 ± 10	0.40
Donor sex (M/F)	34 (42%)/47 (58%)	28 (35%)/53 (65%)	0.33
Donor type (living/deceased)	64 (79%)/17 (21%)	69 (85%)/12 (15%)	0.31
HLA mismatches	3.0 ± 1.3	2.8 ± 1.4	0.65
Follow-up period (IQR) (mo)	96 (68–155)	100 (76–146)	0.78
Initial immunosuppressive treatment, n (%)			
CNI/MMF/PRD	14 (67)	16 (76)	0.50
CNI/AZA/PRD	7 (33)	5 (24)	
Maintenance immunosuppressive treatment, n (%)			
CNI/MMF/PRD	11 (52)	13 (62)	
CNI/AZA/PRD	5 (24)	5 (24)	0.54
mTORi/AZA/PRD	2 (10)	—	
MMF/PRD	3 (14)	3 (14)	
Laboratory characteristics during follow-up			
Median hsCRP (IQR) (mg/L)	12.6 (7.3–18.7)	5.7 (3.8–8.8)	0.002
Mean ESR (mm/h)	35.2 ± 11.6 (7.5–56)	21.6 ± 7.4 (6–24)	<0.001
Laboratory characteristics at last follow-up			
Serum creatinine (mg/dL)	1.9 ± 0.9	1.4 ± 0.4	0.16
Serum albumin (g/dL)	3.6 ± 0.8	4.5 ± 0.4	0.03
eGFR (mL/min per 1.73 m^2)	53.5 ± 31.2	67 ± 20.7	0.30
Proteinuria (IQR) (g/24 h)	0.89 (0.59–3.45)	0.17 (0–0.19)	0.003

AA, amyloid A; AZA, azathioprine; BMI, body mass index; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; F, female; HLA, human leukocyte antigen; hsCRP, high-sensitive *C*-reactive protein; IQR, interquartile range; M, male; MMF, mycophenolate mofetil/sodium; mTORi, mammalian target of rapamycin inhibitor; PRD, prednisone.

TABLE 3.

Study outcomes of AA amyloidosis and control groups

	AA amyloidosis (group 1) (n = 81)	Control group (group 2) (n = 81)	*P*
Rejection episodes, n (%)	11 (13.6)	19 (23.5)	0.11
Overall graft failure (noncensored for death), n (%)	25 (30.9)	12 (14.8)	0.015
Overall death-censored graft failure, n (%)	14 (17.3)	12 (14.8)	0.67
Overall mortality, n (%)	11 (13.6)	—	0.001

AA, amyloid A.

TABLE 4.

Study outcomes of recurrent and nonrecurrent AA amyloidosis groups

	AA amyloidosis (group 1a) (n = 21)	Control group (group 1b) (n = 21)	*P*
Rejection episodes, n (%)	4 (19)	6 (28.6)	0.47
Overall graft failure (noncensored for death), n (%)	9 (42.9)	5 (23.8)	0.19
Overall death-censored graft failure, n (%)	6 (28.6)	3 (14.3)	0.26
Overall mortality, n (%)	3 (14.3)	2 (9.5)	0.63

AA, amyloid A.

Although not reaching statistically significance, overall, 5- and 10-year graft survival rates of group 1a (57.1%, 94.7%, and 53.8%, respectively) were lower than group 1b (76.2%, 95%, and 77.8%, respectively) (P = 0.19, P = 0.95, and P = 0.27) (Table 4) (Figure 1B). The causes of allograft loss in group 1a (9 [42.9%]) were reported to be related to recurrent amyloidosis in 5 patients (23.8%), death with functioning graft in 3 patients (14.3%), and sepsis in 1 patient (4.8%). In group 1b (5 [23.8%]), chronic antibody-mediated rejection in 3 (14.3%) and death with functioning graft in 2 patients (9.5%) caused allograft loss. In group 1a, overall and 5-year death-censored graft survival rates (71.4% and 94.7%, respectively) were similar to group 1b (85.7% and 100%, respectively) (P = 0.26 and P = 0.32, respectively). Although not reaching statistical significance, 10-year death-censored graft survival rates were lower in group 1a (63.6%) compared with group 1b (100%) (P = 0.08).

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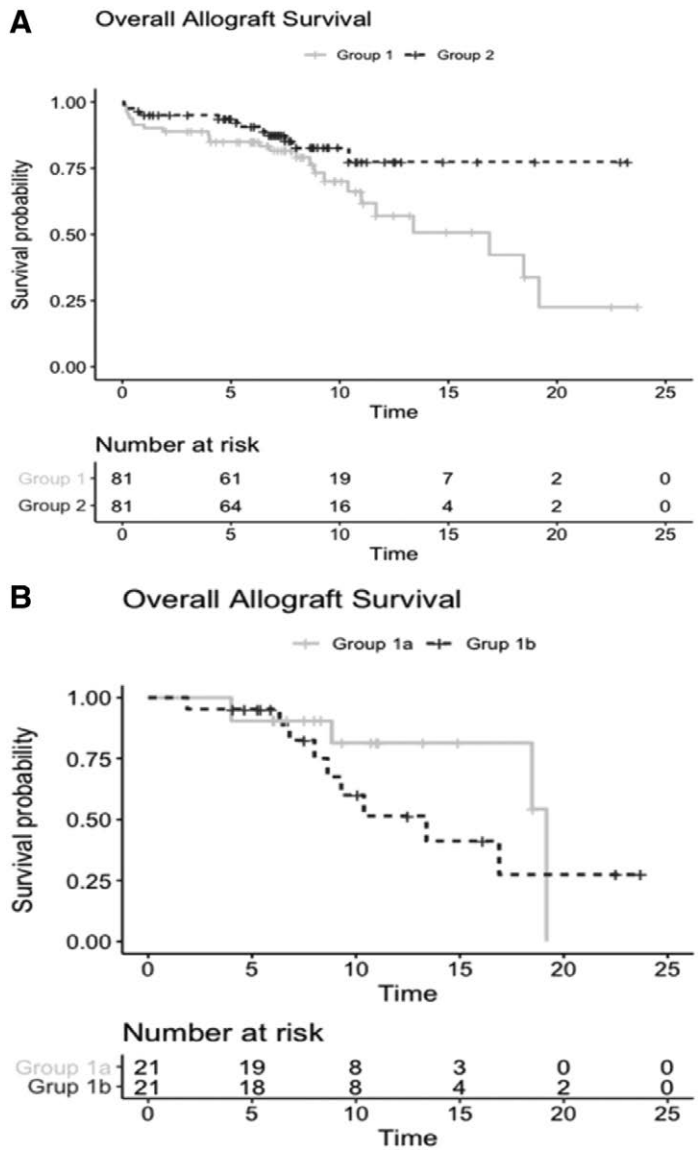

FIGURE 1. A, Kaplan-Meier estimates of allograft survival in amyloid A (AA) amyloidosis (group 1) and control (group 2) groups. B, Kaplan-Meier estimates of overall allograft survival in recurrent AA amyloidosis (group 1a) and nonrecurrent AA amyloidosis (group 1b) groups.

Recipients with FMF-associated AA amyloidosis (group 1) were characterized by an increased risk of death compared with nonamyloidosis recipients (group 2) (11 [13.6%] versus 0%; $P = 0.001$ [hazard ratio, 0.864; 95% confidence interval, 0.793-0.942]) (Table 3). Overall, 11 patients (13.6%) in the amyloidosis group died. Causes of death were sudden cardiac arrest (n = 5), sepsis (n = 2), liver failure (n = 2), major bleeding from gastrointestinal system (n = 1), and non-Hodgkin lymphoma (n = 1). Kaplan-Meier analyses revealed that overall, 5- and 10-year patient survival rates in group 1 (86.4%, 92.5%, and 70.4%) were significantly lower than in group 2 (100%, 100%, and 100%) ($P = 0.001$, $P = 0.026$, and $P = 0.023$, respectively) (Figure 2A). Overall, 5- and 10-year patient survival rates of group 1a (85.7%, 100%, and 80%, respectively) and group 1b (90.5%, 95%, and 80%, respectively) did not differ significantly ($P = 0.63$, $P = 0.34$, and $P = 0.99$, respectively) (Figure 2B). The causes of death were sepsis (n = 1), sudden cardiac arrest (n = 1), and liver failure (n = 1) in group 1a and sudden cardiac arrest (n = 2) in group 1b.

In multivariate Cox regression analysis, age, body mass index, donor type, donor sex, donor age, number of HLA mismatch, posttransplantation biopsy-confirmed rejection, posttransplant mean ESR, and mean hsCRP did not predict primary outcomes.

DISCUSSION

In this study, we present the results of our retrospective, propensity score–matched cohort analysis assessing posttransplant outcomes for renal transplant recipients due to FMF-associated AA amyloidosis. We showed that AA amyloidosis was significantly associated with higher rate of mortality compared with control recipients, while posttransplantation rejection and death-censored graft loss rates were similar in both groups. These findings suggest that patients, whose primary diseases were AA amyloidosis, suffer from lethal complications after transplantation compared with the patients with other causes of ESKD. Five-year survival rate in the present AA amyloidosis

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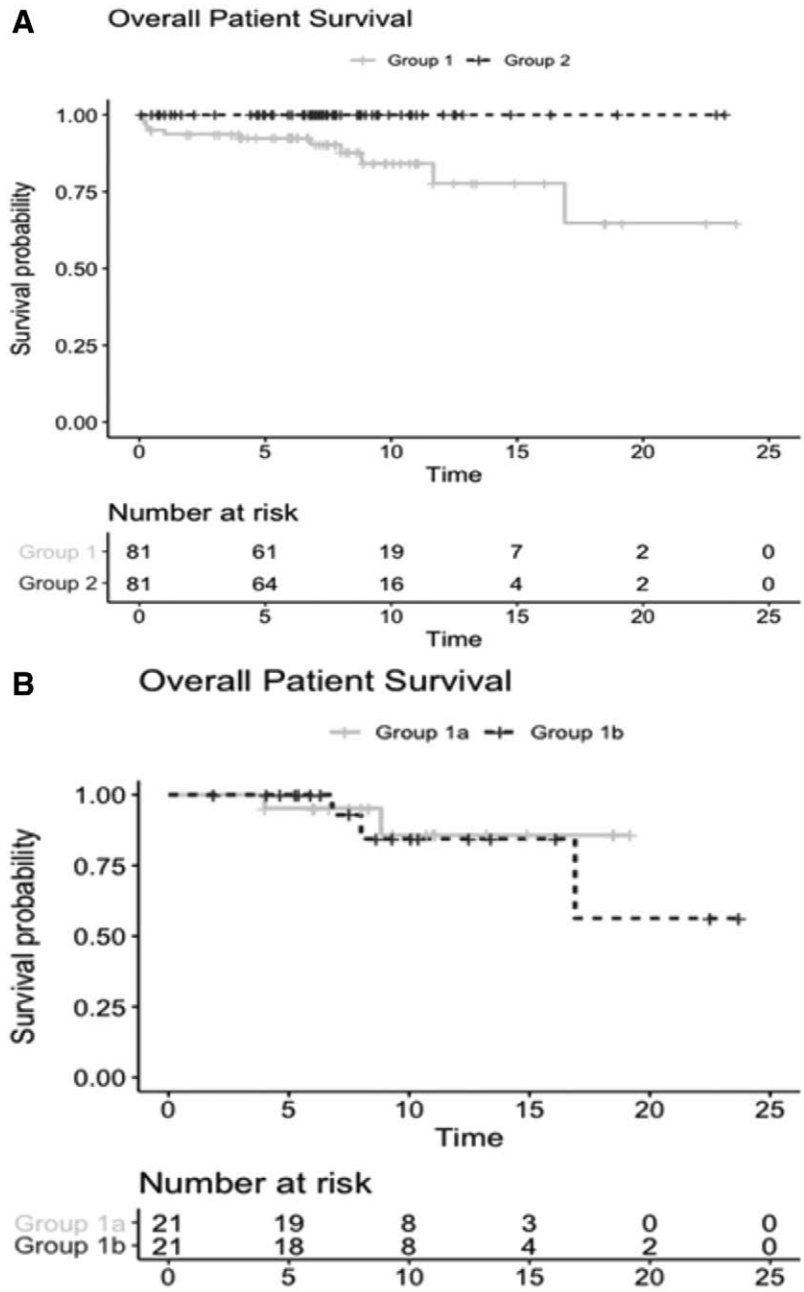

FIGURE 2. A, Kaplan-Meier estimates of patient survival in amyloid A (AA) amyloidosis (group 1) and control (group 2) groups. B, Kaplan-Meier estimates of patient survival in recurrent AA amyloidosis (group 1a) and nonrecurrent AA amyloidosis (group 1b) groups.

cohort is better than previously reported 5-year patient survival rates of 82.5% in AA amyloidosis patients,[7] 73% in FMF-associated AA amyloidosis patients,[8] and 70% in amyloidosis patients.[9] However, mean or median age of the patients in these publications (44.1 ± 12, 43.8 ± 14, 57 [median], respectively) was higher than our cohort, and younger age of our cohort might have contributed to better survival rates compared with previous studies.[7-9]

ESKD caused by AA amyloidosis is associated with higher rates of patient mortality when compared with other causes of ESKD in the general dialysis population.[15] Therefore, transplantation has been considered in these patients, and it has been noted that transplantation offers significant survival benefit when compared with dialysis in these patients.[7] However, increased risk of mortality still remains a concern after kidney transplantation, as shown in the present study.

The leading causes of AA amyloidosis in the Turkish population are FMF and tuberculosis. Thus, our group has published several articles on outcomes of transplantation in these patients since the 1990s.[16-19] We recently reported lower patient survival rate in patients with AA amyloidosis when compared with transplant recipients with chronic glomerular diseases; however, graft survival and rejection rates were similar.[19] Although recurrence of amyloidosis is an important concern, data on this complication are very scarce. Thus, the results of this retrospective propensity score–matched cohort analysis add new knowledge to our understanding of recurrent AA amyloidosis after renal transplantation.

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Amyloidosis development has been shown to correlate with inflammatory markers including hsCRP and SAA levels.[4,20,21] In the present study, mean hsCRP and ESR levels were both found to be significantly higher in patients with AA amyloidosis. Furthermore, patients with recurrent AA amyloidosis have even higher mean hsCRP and ESR levels than nonrecurrent amyloidosis patients. ESR and hsCRP are general markers for inflammation and infection, and our results suggest that monitoring these markers in renal transplantation recipients with FMF amyloidosis may provide additional information about the effects of ongoing inflammation due to amyloidosis on allograft function. On the other hand, these inflammatory markers may not always be strictly parallel in predicting the ultimate outcome, as has been the case in the multivariate analysis of the present study; that is, mean ESR and hsCRP levels did not predict our primary outcome. Also, it is likely that elevation in ESR may be associated with increased levels of fibrinogen and possibly decreased albumin concentration in patients with recurrent amyloidosis.[22]

AA amyloidosis is an ongoing inflammatory process, and renal deposition affects the clinical course and outcome. Effective anti-inflammatory treatment is the only option in preventing further systemic deposition and recurrence of amyloid in allografts. Colchicine is the recommended anti-inflammatory medication in FMF, and a dose of 1.5–2 mg/day has been suggested to prevent and/or delay development of AA amyloidosis.[23] In the present study, most of the patients were receiving appropriate doses of colchicine, yet it did not prevent recurrence in the allograft. Colchicine toxicity is another concern in renal transplant patients and can be hard to manage without lowering suggested doses for effective prophylaxis. Cytochrome P450 3A4 or P-glycoprotein inhibitors like cyclosporine can increase the serum concentration of colchicine.[24] Anti-interleukin-1 therapy (anakinra), which can even reverse proteinuria,[25] is the second-line treatment in patients with FMF, who are intolerant or not responding to colchicine.[26] In the present study, only 6 patients (28.6%) in recurrence AA amyloidosis were converted to anakinra treatment after the diagnosis of allograft AA amyloidosis. The effects of this agent in the renal transplant setting are not well defined. Over-immunosuppression may be a concern, although there is not enough experience on this issue. Certainly, more studies are needed to confirm the efficacy of this newer agent.

This study suffers from several limitations. First, the study is retrospective, so only preexisting data were analyzed. Second, number of patients in the study is quite low; however, to the best of our knowledge, even this limited number of patients makes the present study the largest series documenting recurrence in the transplant patients. The largest study in the literature had a total number of 59 patients, and only 8 of them had recurrent AA amyloidosis.[7] The third limitation of the study is the lack of protocol biopsies in control groups; thus, recurrence of the amyloidosis may be underdiagnosed in group 2. Finally, the fourth limitation is that the control group had 100% survival throughout the study, which might have caused an overestimation of the relative mortality risk in transplant recipients with AA amyloidosis.

In conclusion, AA amyloidosis is significantly associated with mortality after transplantation. Extracellular deposition of AA amyloidosis in several extrarenal organs might have resulted in this increased mortality. Pretransplant cardiac evaluation of these patients remains a key clinical priority. Recurrence of AA amyloidosis after transplantation is associated with increased inflammation. Inflammatory indicators should be monitored closely, and persistent high levels of acute-phase reactants should raise concerns about amyloid recurrence.

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