Chronic Active Antibody-Mediated Rejection and Kidney Allograft Survival: A 14-Year Single-Center Retrospective Analysis

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Abstract

Background: Chronic active antibody-mediated rejection (ABMR) is a significant cause of graft loss in kidney transplants. The current treatment strategies have not been very effective. The present study examined kidney allograft survival after diagnosis and treatment of chronic active ABMR and explored factors associated with allograft survival.

Methods: 144 kidney transplants were identified from 2007 to 2021. Thirty patients had ABMR, and 15 cases in 12 patients were classified as having chronic active ABMR according to the 2017 Banff classification.

Results: The average time from transplantation to the diagnosis of chronic active ABMR was six years. The median graft survival after the diagnosis was 2.6 years. Fifty-eight percent of the patients lost their grafts. The average serum creatinine and urine protein/creatinine ratio at the time of diagnosis of chronic active ABMR were 2.6 mg/dL and 1.5 g/g, respectively. Higher serum creatinine was the only factor significantly associated with graft failure. The association between heavier proteinuria and graft loss was also noted, but the difference did not reach statistical significance.

Conclusion: Chronic active ABMR was associated with poor graft survival. Decreased allograft function at diagnosis was significantly associated with graft failure.

Keywords: renal transplant; chronic rejection; kidney transplantation; renal transplantation

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ภาวะปฏิเสธไตจากแอนติบอดีแบบเรื้อรังและต่อเนื่อง และอัตราการรอดของไตที่ได้รับการปลูกถ่าย: การวิเคราะห์ย้อนหลัง 14 ปีในโรงพยาบาลแห่งเดียว

พิชญา แก้วเพิ่ม, ปิยะวดี หอมไกรลาศ

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บทคัดย่อ

บทนำ: ภาวะปฏิเสธไตจากแอนติบอดีแบบเรื้อรังและต่อเนื่องเป็นหนึ่งในสาเหตุสำคัญของการสูญเสียไตที่ได้รับการปลูกถ่าย ในปัจจุบันการรักษาภาวะดังกล่าวยังไม่ค่อยได้ผลดีเท่าที่ควร การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาการอยู่รอดของไตหลังจากที่ได้รับการวินิจฉัยและรักษาภาวะปฏิเสธไตจากแอนติบอดีแบบเรื้อรังและต่อเนื่อง แลปัจจัยที่เกี่ยวข้องกับการสูญเสียไต

ระเบียบวิธีวิจัย: มีผู้ที่ได้รับการปลูกถ่ายไตระหว่างปี พ.ศ. 2550 ถึง 2564 จำนวน 144 ราย พบว่ามีภาวะปฏิเสธไตจากแอนติบอดีจำนวน 30 ราย และมีภาวะปฏิเสธไตจากแอนติบอดีแบบเรื้อรังและต่อเนื่องที่วินิจฉัยได้จากผลชิ้นเนื้อไตตามเกณฑ์การวินิจฉัยของ Banff ปี ค.ศ.2017 จำนวนทั้งสิ้น 15 ครั้งในผู้ป่วย 12 ราย

ผลการศึกษา: ระยะเวลาโดยเฉลี่ยตั้งแต่การปลูกถ่ายไตถึงการวินิจฉัยภาวะปฏิเสธไตจากแอนติบอดีแบบเรื้อรังและต่อเนื่องคือ 6 ปี ระยะเวลาการอยู่รอดของไตหลังจากได้รับการวินิจฉัยคือ 2.6 ปี โดยมีอัตราการสูญเสียไตอยู่ที่ร้อยละ 58.3 ผู้ป่วยที่ได้รับการวินิจฉัยว่ามีภาวะปฏิเสธไตจากแอนติบอดีแบบเรื้อรังและต่อเนื่องมีค่าคริเอทินิน 2.6 มก/ดล และมีอัตราส่วนของปริมาณโปรตีนในปัสสาวะ/คริเอทินิน 1.5 กรัม/กรัม ปัจจัยเดียวที่พบว่ามีความสัมพันธ์กับการสูญเสียไตอย่างมีนัยสำคัญทางสถิติ คือ ค่าคริเอทินินที่สูงในตอนที่ได้รับวินิจฉัย และพบแนวโน้มความสัมพันธ์ของปริมาณโปรตีนที่รั่วในปัสสาวะที่สูงกับการสูญเสียไต แต่ไม่มีนัยสำคัญทางสถิติ

สรุป: ภาวะปฏิเสธไตจากแอนติบอดีแบบเรื้อรังต่อเนื่องส่งผลต่อทำให้อัตราการอยู่รอดของไตที่ลดลง การทำงานของไตที่ลดลงตอนที่ได้รับการวินิจฉัยเป็นปัจจัยเดียวที่มีความสัมพันธ์กับการสูญเสียไต

คำสำคัญ: เปลี่ยนไต; สลัดไต; ภูมิคุ้มกัน; สลัดไตเรื้อรัง

Introduction

Kidney transplantation is the best modality of renal replacement therapy for patients with end-stage kidney disease (ESKD). Improvements in kidney matching algorithms and effective immunosuppressive drug regimens result in a continual increase in allograft survival. Nevertheless, the rates of 10-year allograft survival remain low at 50% for deceased donor recipients and 65 % for living donor recipients.[1] The most common cause of graft failure is death with a functioning graft, accounting for 51% and 53% of graft failure in living donor and deceased donor recipients, respectively. The second most common cause of graft failure is chronic rejection.[2]

Chronic antibody-mediated rejection (ABMR) is responsible for as high as 60% of late graft failures. An effective management strategy is crucial in improving long-term graft outcomes.[3] This type of rejection can be divided into two groups: chronic active ABMR, where the

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allograft is continuously attacked by antibodies, leading to ongoing inflammation, and chronic ABMR, when antibodies have previously attacked the allograft but are no longer actively doing so. The symptoms of chronic active ABMR are insidious, presenting as proteinuria and a gradually rising serum creatinine. Despite being a major cause of allograft failure, an effective treatment has yet to be established.[4] The retrospective study investigated allograft outcomes after chronic active ABMR treatment and factors associated with graft survival in chronic active ABMR.

Materials and Methods

Study design and ethics Statement

This retrospective study was conducted at Bhumibol Adulyadej Hospital, Bangkok, Thailand. All patients who underwent living-related or deceased-donor kidney transplantation between 2007 and 2021 were included. The ethics committee approved the study for human research of Bhumibol Adulyadej Hospital. Informed consent was not required.

Patients and diagnosis of chronic active ABMR

The electronic medical records were reviewed. Among the 144 kidney transplant recipients, 30 patients had biopsy-proven ABMR. Patients with only chronic active ABMR were identified according to the 2017 Banff classification. The criteria required the presence of ABMR (evidence of current or recent antibody interaction with the endothelium (C4d), or serologic evidence of donor-specific antibody (DSA), microvascular inflammation (MVI), qualifying for this category is a glomerulitis (g) score + peritubular capillaritis (PTC) score ≥ 2) with histologic evidence of chronic tissue injury, such as transplant glomerulopathy (TG) attributable to ABMR. Patients with compatible histology but negative DSA were included in the analysis as suspected chronic active ABMR. A total of 15 chronic active ABMR cases in 12 patients were included in the final analysis.

Biochemical and treatment data

The data on serum creatinine, proteinuria, donor-specific human leukocyte antigen (HLA) antibody development, dates of transplantation and allograft biopsy, and the treatment received post-biopsy were recorded. Additional data, including age, gender, primary kidney disease, panel reactive antibody (PRA), donor type, HLA mismatching, early complications, medications, and immunosuppression drug levels, were also collected. The treatment for chronic active ABMR was decided based on the clinical condition and the decisions made by the primary nephrologist. At our center, all patients diagnosed with chronic active ABMR received five sessions of plasma exchange (1.5 x blood volume) followed by intravenous immunoglobulins (IVIG) infusion (2g/kg). In patients with severe rejection, rituximab 375 mg/m^2 was also administered.

Outcomes

The primary outcome was renal allograft survival. The secondary outcome was factors associated with allograft survival. Graft loss was defined as the need to return to dialysis. Patients were followed until graft loss, death, or the end of 2023.

Sample size calculation

The sample size was calculated according to the previous study on treatment of chronic active ABMR in renal transplant recipients.[5] The calculation yielded a sample size of 19 patients.

$$N = [Z\alpha_2/\varepsilon]^2$$
$$\varepsilon = \left|\frac{\hat{\lambda}-\lambda}{\lambda}\right|$$
$$S(t) = e^{-\lambda t}$$
$$\lambda = -ln(S)/time$$
$$\text{Alpha } (\alpha) = 0.05,\ z_{/2} = 1.959964$$

λ = Median overall graft survival 5.6 years = (-log(0.5)/5.6) = 0.1238

$\hat{\lambda}$ = 1/total time follow up 15 years = 1/15 = 0.067

ε = |(0.067– 0.1238)/ 0.1238| = 0.4588

N = 19

Statistical Analyses

The data were reported as number (%), mean ± standard deviation, or median (interquartile range). Differences between groups were analyzed using

Student's t-test, Wilcoxon rank-sum test, or Fisher's exact test. Allograft survival was analyzed using the Kaplan-Meier curve. All analyses were performed using R version 4.1.1. P value <0.05 was considered statistically significant.

Results

Baseline characteristics

The study flow diagram is shown in **Figure 1.** The patients with chronic active ABMR were 75% males with an average age of 41 years. Sixteen percent had diabetes, 58% had hypertension, and 58.3% had chronic glomerulonephritis as the cause of ESKD. The mean PRA at the time of transplantation was 0%. Fifty percent received kidneys from living donors. Early rejection, defined as any rejection within three months after kidney transplantation, was observed in 25%, while 25% experienced delayed graft function. **Table 1** shows the baseline characteristics of all patients.

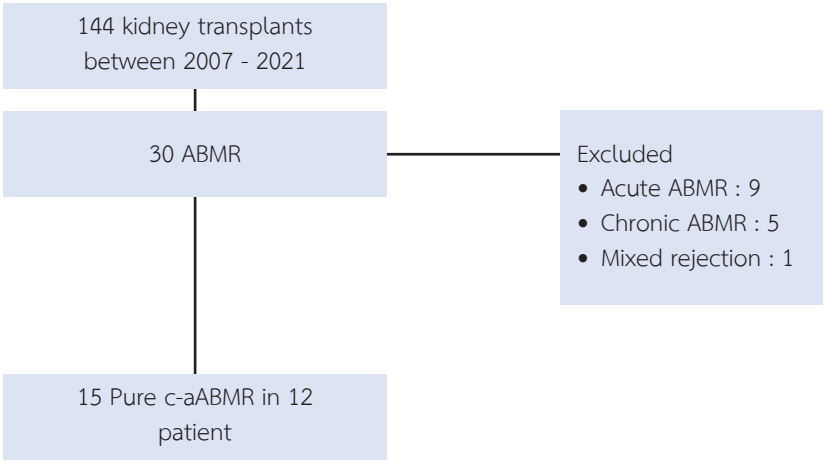

Figure 1 Study Flow Diagram
ABMR, antibody-mediated rejection; c-aABMR, chronic active ABMR

Table 1 Baseline biochemical data of all patients

Parameters	N=12
Male sex, N (%)	9 (75)
Age (years)	41.4 ± 9.1
Underlying disease, N (%)	
• Diabetes mellitus • Hypertension • Dyslipidemia	2 (16) 7 (58) 3 (25)
Cause of end-stage kidney disease, N (%)	
• Unknown • Chronic glomerulonephritis • Autosomal dominant polycystic kidney disease • IgA Nephropathy	7 (58.3) 2 (16.7) 2 (16.7) 1 (8.3)
Donor parameters	
• Living donor, N (%) • Donor age (years)	6 (50) 40.4 ± 11.8

Parameters	N=12
Immunological risk	
• HLA mismatching	3.5 (2-6)
• Panel reactive antibody (%)	0 (0-0)
Early complications, N (%)	
• Delayed graft function, N (%)	3 (25)
• Early rejection, N (%)	3 (25)
Immunosuppressive drugs, N (%)	
• Tacrolimus	6 (50)
• Cyclosporine	2 (16.7)
• Mycophenolate mofetil	11 (91.7)
• Prednisolone	12 (100)
• Everolimus	5 (41.7)
Drug levels (ng/ml)	
• Tacrolimus	4.3 ± 1.5
• Cyclosporine	206 ± 220.6
• Everolimus	7.2 ± 1.4
Parameters at the time of diagnosis of chronic ABMR	
• Duration after transplantation (month)	74.3 ± 51.2
• Serum creatinine (mg/dL)	2.6 ± 0.7
• Spot urine protein/creatinine (g/g)	1.5 ± 1.6
• Positive donor-specific antibody, N (%)	9 (75)
HLA class 1	4 (44.4)
HLA class 2	7 (77.8)
Mean fluorescent intensity	7425 (3551-8610)
Treatment, N (%)	
• Plasma exchange	10 (83.3)
• Intravenous gamma globulin	10 (83.3)
• Rituximab	3 (25)
• Repeated treatment	3 (25)
• Supportive treatment	2 (16.7)

HLA, human leukocyte antigens

Histopathology

The average duration from transplantation to the diagnosis of chronic active ABMR was 74.3 ± 51.2 months. **Table 2** illustrates histopathological features of chronic active ABMR according to Banff classification. The median g score was 2, the mean PTC score was 2.3, and the mean c4d score was 2.1. The median scores for interstitial inflammation, tubulitis, and intimal arteritis were 0. The mean chronic glomerulopathy (Cg) score was 1.5. The median scores for interstitial fibrosis, tubular atrophy, and increased mesangial matrix were 1. The mean arteriolar hyalinosis was 0.9.

Table 2 Histopathological features of chronic active antibody-mediated rejection according to Banff classification

Characteristics	Banff's score
Interstitial Inflammation (i)	0 (0-1)
Tubulitis (t)	0 (0-0)
Intimal arteritis (v)	0 (0-0)
Glomerulitis (g)	2 (1.5-2)
Peritubular capillaritis (PTC)	2.3 ± 0.6
C4d	2.1 ± 1.5
Interstitial fibrosis (ci)	1 (1-1)
Tubular atrophy (ct)	1 (1-1.5)
Chronic glomerulopathy (cg)	1.5 ± 0.8
Mesangial matrix increase (mm)	1 (0.5-1)
Arteriolar hyalinosis (ah)	0.9 ± 0.7
Ci + Ct	2.3 ± 0.8
g + PTC	4.1 ± 0.9

Donor-specific antibody

Nine of 12 patients (75%) had the data on DSA. Most patients showed MHC class II DSA (77.8%), either alone or in combination with other types of MHC. The median mean fluorescence intensity was 7425.

Treatment

Ten of 12 patients (83%) received IVIG and plasma exchange treatments. Three of these ten patients (30%) also received rituximab. Two patients (16.7%) did not receive the treatment because of rapidly deteriorating allograft function (increased serum creatinine from 3.5 mg/dL to 4.5 mg/dL within one week and heavy proteinuria of 6.4 g/g) and the presence of active infection (intraabdominal abscess). Among these two patients, the primary nephrologist chose to optimize the immunosuppressive drugs.

Repeated biopsies were performed on three patients who subsequently received a repeated course of treatment. Two patients underwent repeated biopsies due to worsening allograft function, and both eventually developed allograft failure. The other patient had a repeated biopsy due to increasing proteinuria. The allograft function of this patient remained stable during the 4-year follow-up period.

Graft survival

Patients were followed for a median of 7 years (5.5-9.8 years). Seven of 12 patients (58.3%) lost their graft. The median graft survival from transplantation was 9.5 years **(Figure 2A)**. The median graft survival from the diagnosis of chronic active ABMR was 2.6 years **(Figure 2B)**. The graft survival rates were as follows: 1-year survival 100% (95% confidence interval 100-100), 5-year survival 83% (64.7-100), and 10-year survival 44% (22.4-88.2).

Patients with graft failure had significantly higher baseline serum creatinine (2.9 vs. 2.1 mg/dL; p-value = 0.032) and lower eGFR (24.7 vs. 35.8 mL/min/1.73m^2; p-value = 0.044) at the time of allograft biopsy compared to patients with functioning graft. Patients with higher urine protein (1.3 vs. 1 g/g; p-value = 0.087) showed a tendency toward an increased risk of graft loss. Banff classification score did not predict graft failure. However, higher scores for PTC, c4d, and cg were associated with worse graft survival **(Table 3 and Figure 3)**

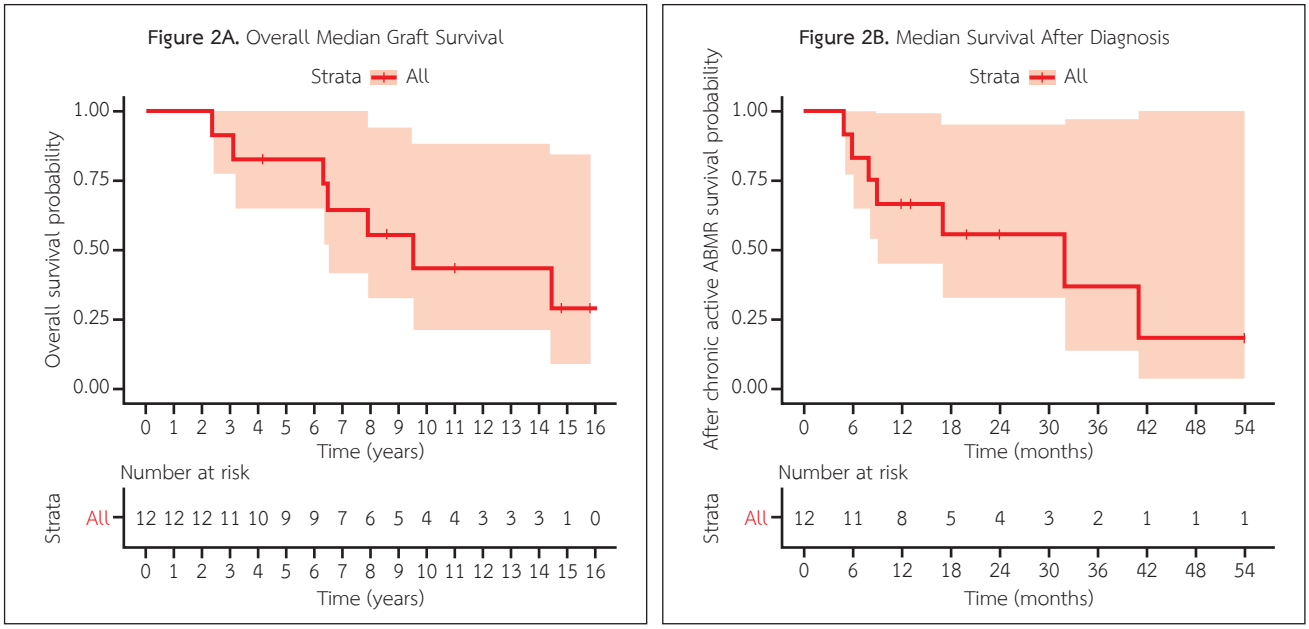

Figure 2 Graft survival.

Figure 2A, graft survival from the time of transplantation; **Figure 2B**, graft survival from the time of diagnosis.

Table 3 Factors associated with graft failure at the time of allograft biopsy

Factors	Kidney Allograft		P-value
	Failure (N=7)	Functioning (N=5)	
Serum creatinine (mg/dL)	2.9 ± 0.7	2.1 ± 0.2	0.032
Estimated GFR (mL/min/1.73 m^2)	24.7 ± 9.1	35.8 ± 6.7	0.044
Urine protein/creatinine (g/g)	1.3 (1-2.1)	1 (0.5-1.2)	0.087
Histopathology			
Interstitial Inflammation (i)	0 (0-1)	0 (0-8)	0.832
Tubulitis (t)	0 (0-0)	0 (0-0)	0.273
Intimal arteritis (v)	0 (0-0)	0 (0-0)	0.496
Glomerulitis (g)	2 (2-2)	2 (1.2-2)	0.893
Peritubular capillaritis (PTC)	2.4 ± 0.5	2 ± 0.6	0.163
C4d	2.4 ± 1.5	1.5 ± 1.4	0.242
Interstitial fibrosis (ci)	1 (1-1)	1 (1-1.8)	0.5
Tubular atrophy (ct)	1 (1-1)	1 (1-1.8)	0.7
Chronic glomerulopathy (cg)	1.7 ± 1	1.3 ± 0.5	0.469
Mesangial matrix increase (mm)	1 (1-1)	1 (0.2-1)	0.701
Arteriolar hyalinosis (ah)	0.8 ± 0.7	1 ± 0.9	0.59
Ci+Ct	2.2 ± 0.4	2.5 ± 1.2	0.539
g + PTC	4.3 ± 0.7	3.8 ± 1.20	0.318

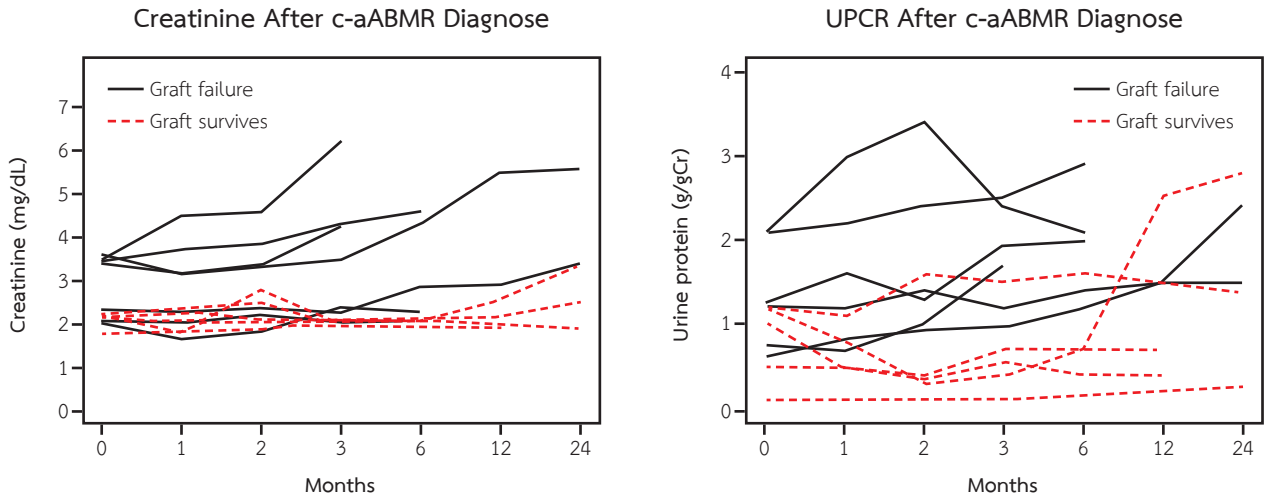

Figure 3 Serum creatine and urine protein after the diagnosis of chronic active antibody-mediated rejection and allograft survival

Discussion

The present study described a series of kidney transplant recipients with chronic active ABMR. The incidence of chronic active ABMR was 8%. The average duration from kidney transplantation to the diagnosis was 6.3 ± 4.3 years. Among the patients with chronic active ABMR, 58.3% of patients lost their kidney allografts. The median graft survival from the time of diagnosis was 2.6 years. Higher serum creatinine and lower eGFR at the time of allograft biopsy predicted worse graft survival. A trend between higher urine protein and decreased graft survival was also noted.

The previous study by Redfield et al. reported a 7% incidence of chronic active AMBR among their patients.[6] The incidence of graft loss was 76%, with the median graft survival from the diagnosis being 1.9 years. These findings are comparable to the present study. Moreover, this previous study also demonstrated the association between serum creatinine >3 mg/dL and urine protein >1 g/g with a higher risk of graft loss. Again, these findings are consistent with the present study. Another study by Yilmaz et al. reported a lower incidence of 2.5% of chronic active ABMR with graft survival rates of 97%, 85%, 73%, and 50% at 1, 3, 5, and 10 years, respectively.[7] Serum creatinine levels ≥3 mg/dL, estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2, and urine protein ≥1 g/g at the time of diagnosis were associated with ineffective treatment and decreased graft survival rate.

However, the study by Chiu et al. reported considerably better graft survival.[5] The median graft survival after the diagnosis was 5.6 years, with only 26.8% of the patients losing their allografts. These differences could be attributed to the early detection of ABMR in the study by Chiu et al.. Chronic active ABMR was diagnosed when serum creatinine was below 1.8 mg/dL. Moreover, the patients in this study received multiple follow-up biopsies and multiple repeated treatment courses if the biopsy results showed persistent lesions. These data suggested that an aggressive monitoring method through protocol biopsy rather than serum creatinine and repeated courses of treatment according to the biopsy findings could result in a more favorable allograft outcome.

The present study did not find a significant difference in the immunological and histopathology features between the patients with graft failure and functioning grafts. This was likely due to the small number of patients. However, the group that experienced graft failure did show a tendency toward higher scores of PTC, C4d, cg, and MVI. These are consistent with the findings from Sapinar et al.[8] In this previous study, the improvements in histopathology after treatment included a significant decline in PTC score and glomerulitis. In addition, Yilmazet et al. reported that transplant glomerulopathy was a poor prognostic factor for allograft outcome.[7]

The present study is limited by being a single-center and retrospective study, which limits the conclusion regarding causality. The small number of cases also diminishes the statistical power, especially in analyzing the differences in the immunologic and histology features.

In conclusion, the incidence of chronic ABMR was 8% and was associated with decreased graft survival. Decreased allograft function at diagnosis was a poor prognostic factor for allograft survival. Early and more aggressive treatment and monitoring may be warranted to improve the outcome of chronic active ABMR.

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