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The Prognostic Significance of Banff Classification Lesions in Determining Renal Allograft Survival During Chronic Active Antibody-mediated Rejection

Kronik Aktif Antikor Aracılı Rejeksiyonda Banff Lezyonlarının Böbrek Allograft Sağkalımına Etkileri

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Abstract

Objective: Chronic active antibody-mediated rejection (ca-ABMR) has been identified as a primary cause of graft loss in kidney transplant recipients over an extended period. The outcomes of intravenous immunoglobulin and plasmapheresis treatments in ca-ABMR are controversial; therefore, no established effective treatment has yet been found. This study aims to identify the clinical and histopathological parameters that influence the decision to treat or not treat ca-ABMR cases.

Methods: Fourteen patients diagnosed with ca-ABMR, who underwent biopsy with a pre-diagnosis of kidney rejection between 2018 and 2024 at the pathology department, were included in the study. The histopathological features were evaluated using the Banff 2019 criteria.

Results: 28.6% of the patients (n=4) were female, and 71.4% (n=10) were male. The mean age of male patients was 46.40±12.63 years, while the mean age of female patients was 33.00±16.39 years. The average time from kidney transplantation to biopsy was 56.85±47.27 months. No statistically significant differences were found between the treated (n=10) and untreated (n=4) groups in terms of microvascular inflammation score (p=0.88), chronic tissue damage score (p=0.87), transplant glomerulopathy (p=0.99), intimal arteritis (p=0.99), and immunohistochemical C4d staining score (p=0.50). However, the high-risk group for microvascular inflammation (glomerulitis+peritubular capillaritis) had a significantly longer survival time than the low-risk group (p=0.03 <0.05). No statistically significant difference in survival time was found between the low- and high-risk groups for chronic tissue damage (tubular atrophy+interstitial fibrosis+total inflammation) score, (p=0.56 >0.05). No statistically significant differences were found in Banff lesion scores between the treated and untreated groups.

Conclusion: The early detection of graft histopathological changes, often achieved through protocol biopsies, facilitates the identification of ca-ABMR patients who will respond favorably to treatment.

Keywords: Banff lesions, chronic active antibody-mediated rejection, microvascular inflammation, renal transplantation

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Öz

Amaç: Kronik aktif antikor aracılı rejeksiyon (ca-ABMR), böbrek nakli alıcılarında uzun vadede greft kaybının önde gelen nedenlerinden biridir. ca-ABMR'de intravenöz immünglobulin ve plazmaferez tedavilerinin sonuçları tartışmalı olduğundan, belirlenmiş etkili bir tedavi bulunamamıştır. Bu çalışma, ca-ABMR vakalarını tedavi etme veya tedavi etmeme kararını etkileyen klinik ve histopatolojik parametreleri belirlemeyi amaçlamaktadır.

Yöntem: 2018-2024 yılları arasında patoloji bölümünde böbrek rejeksiyon ön tanısıyla biyopsi yapılan ve kronik aktif antikor aracılı rejeksiyon tanısı konulan on dört hasta çalışmaya dahil edildi. Histopatolojik özellikler Banff 2019 kriterlerine göre skorlandı.

Bulgular: Hastaların %28,6'sı (n=4) kadın, %71,4'ü (n=10) erkekti. Erkek hastaların yaş ortalaması 46,40±12,63 yıl iken, kadın hastaların yaş ortalaması 33,00±16,39 yıl olarak bulundu. Böbrek naklinden biyopsiye kadar geçen ortalama süre 56,85±47,27 ay olarak bulundu. Tedavi edilen (n=10) ve tedavi edilmeyen (n=4) gruplar arasında mikrovasküler inflamasyon skoru (p=0,88), kronik doku hasarı skoru (p=0,87), transplant glomerulopatisi (p=0,99), intimal arterit (p=0,99) ve immünohistokimyasal C4d boyanma skoru (p=0,50) açısından istatistiksel olarak anlamlı bir fark saptanmadı. Ancak mikrovasküler inflamasyon açısından yüksek riskli grup (glomerulit+peritübüler kapillerit), düşük riskli grupla karşılaştırıldığında anlamlı derecede daha uzun bir sağkalım süresine sahipti (p=0,03 <0,05). Kronik doku hasarı (tübüler atrofi+interstisyel fibrozis+toplam inflamasyon) skoru için düşük ve yüksek risk grupları arasında sağkalım süresinde istatistiksel olarak anlamlı bir fark bulunmadı (p=0,56 >0,05). Tedavi edilen ve tedavi edilmeyen gruplar arasında Banff lezyon skorlarında istatistiksel olarak anlamlı bir fark bulunmadı.

Sonuç: ca-ABMR hastalarında, protokol biyopsileri yoluyla greftlerdeki histopatolojik değişikliklerin erken tespiti, tedaviden fayda görecek hastaların belirlenmesine yardımcı olabilir.

Anahtar Kelimeler: Banff lezyonları, kronik aktif antikor aracılı rejeksiyon, mikrovasküler inflamasyon, böbrek nakli

Introduction

Chronic active antibody-mediated rejection (ca-ABMR) is one of the leading long-term causes of graft loss in kidney transplant recipients. There is a lack of consensus regarding the relationship between renal transplant survival and clinical and histopathological findings in ca-ABMR patients[1].

When graft dysfunction develops, graft biopsy is considered the gold standard to identify the underlying pathology. Recently, graft biopsy has been utilized for histopathological and immunohistochemical examination as well as for genetic analysis[2].

The Banff classification, introduced in 1991, has become the most commonly used classification system for kidney transplant pathology. Banff scores are used to grade acute and chronic ABMR, as well as T-cell mediated rejection[3]. In addition to Banff lesions, the diagnosis of ca-ABMR is supported by the presence of circulating donor-specific antibodies (DSA) against donor human leucocyte antigen (HLA) and/or elevated levels of gene transcript/classifier expression within the biopsy specimens, strongly associated with ABMR[2,3].

Despite extensive studies, no Food and Drug Administration-approved treatments for ca-ABMR have shown definitive long-term benefits[4]. The standard treatment today includes plasmapheresis and intravenous immunoglobulin (IVIg) therapy, combined with single or combination therapies such as CD20 monoclonal antibody (rituximab)[5], proteasome inhibitors (bortezomib)[6], anti-IL-6R monoclonal antibody (tocilizumab)[7], and anti-complement monoclonal antibody (eculizumab)[8].

For patients diagnosed with ca-ABMR, the clinically important question is which cases are more likely to respond to treatment and which therapy yields better outcomes. In this study, we aim to analyze the clinical characteristics of ca-ABMR patients with cases confirmed by biopsy and the relationship between the Banff lesion scores in their biopsies and graft survival. By doing so, we aim to identify the clinical and histopathological parameters that influence the decision to treat ca-ABMR cases.

Materials and Methods

Patients and Study Design

This study included 14 patients diagnosed with ca-ABMR histopathologically, who applied to our pathology department with a suspected kidney rejection between 2018 and 2023. Data were collected regarding the patients' age, gender, primary kidney disease, and the source of the kidney graft (living/deceased donor). Follow-up data included serum creatinine (Cr) levels, estimated glomerular filtration rate (eGFR), transplant date, biopsy date, graft loss date, and treatments administered following diagnosis. Graft loss was defined as the initiation of dialysis or death related to transplantation.

Patients aged ≥18 years at the time of transplantation who had undergone kidney transplantation at our center or external centers were included in the study. Patients younger than 18 years old at the time of transplantation, patients undergoing combined organ transplantation (e.g. kidney, liver, pancreas), and patients lacking complete laboratory or clinical data were excluded from the final analysis.

This study was reviewed and approved by the Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (approval number: 16/16, date: 24.10.2024). Informed consent was waived by the institutional review board due to the retrospective nature of the study. This study was presented as an oral presentation at the 15th Congress of the Turkish Transplantation Centers Coordination Association (October 17-20, 2024, Gaziantep).

Histopathology

The histopathological features were evaluated using the Banff 2019 classification, which encompasses both acute and chronic rejection features. According to the 2019 Banff reporting standards, acute Banff lesions are characterized by interstitial inflammation, tubulitis, intimal arteritis (v), glomerulitis (g), peritubular capillaritis (ptc), and the presence of C4d staining. Chronic Banff lesions encompass a range of pathologies, including interstitial fibrosis (ci), tubular atrophy (ct), and the presence of C4d staining, transplant glomerulopathy (cg), and multilayering of the peritubular capillary basement membrane (ptcml)[3].

The 2019 Banff classification mandates that the identification of ca-ABMR is contingent upon histological evidence of both a vascular endothelial response to antibodies (specifically, linear C4d positivity in peritubular capillaries or g+ptc≥2) and concurrent indicators of chronic injury (such as cg, ptcml multilayering, or intimal fibrosis within arteries)[3].

All kidney graft biopsies were performed using a percutaneous technique under ultrasound guidance (2-3 samples per biopsy; 16-gauge needle). Transplant biopsies were examined by light microscopy using histochemical hematoxylin and eosin (HE), Jones HE, Masson's trichrome, periodic acid-schiff, Congo Red stains, and immunofluorescence microscopy for IgG, IgA, IgM, C3, C4d, C1q, fibrinogen, kappa and lambda light chains. C4d staining was applied both by immunofluorescence on frozen sections and by immunohistochemistry on paraffin sections.

HLA antibody testing and gene expression tests are not routinely performed at our hospital. Therefore, in patients who could not be tested for DSA, a positive C4d staining was accepted as the definitive diagnosis of ca-ABMR.

The microvascular inflammation (MVI) score (g+ptc) ≤3 was considered low-risk, ≥4 was considered high-risk[9]. Chronic tissue damage score [ci+ct+total inflammation (ti)] ≤5 was considered low-risk, and ≥6 was considered high-risk[10]. The cg score of 0 or 1 was considered low-risk, and a score of 2 or 3 was considered high-risk.

Statistical Analysis

A comprehensive array of descriptive statistics was employed to present the data, including sample size (n), relative percentages (%), arithmetic means, corresponding standard deviations, medians, absolute ranges, and interquartile range (Q1 and Q3). In instances where the percentage of cells exhibiting an expected value less than 5 was greater than 20%, Fisher's exact test was employed. Conversely, when the percentage was less than 20%, Pearson's chi-square test was utilized. The normality assumption was checked using the Shapiro-Wilk test. For the comparison of numerical data between the two groups, the independent samples t-test was used when the data were normally distributed, and the Mann-Whitney U test was used when the data did not follow a normal distribution. Statistical analyses were performed using SPSS 23.0 software. A p-value of <0.05 was considered statistically significant. To compare survival times between patients who received treatment and those who did not, Kaplan-Meier analysis and the Log-Rank test were applied.

Results

The genders of the patients were: 4 females (28.6%) and 10 males (71.4%). The mean age of the patients was 42.57±14.55 years (19-66 years). The average age of the male patients was 46.40±12.63 years (30-69 years), and the average age of the female patients was 33.00±16.39 years (19-54 years).

The underlying causes leading to end-stage kidney disease in the patients were as follows: 35.7% hypertension, 28.6% diabetes, 14.3% unknown chronic kidney disease, and 21.3% other causes. Among the "other" causes, hypoplastic kidney, familial Mediterranean fever, and systemic lupus erythematosus were identified.

Thirteen patients (92.9%) received a kidney transplant from a living donor, while only one patient (7.1%) received a kidney from a deceased donor. One patient had undergone a second kidney transplant. The average time from transplantation to biopsy was 56.85 ± 47.27 months (7-150 months).

The patients' serum Cr and eGFR values at different time points post-transplantation are presented in Table 1. The most recent Cr level in the patients was 1.80±0.77 mg/dL (range: 1.11-3.30), and the basal eGFR value was 44±10.86 mL/min/1.73m^2 . Note: verify consistency between the stated range and mean for eGFR values. At the time of biopsy, the average serum Cr level was 4.37±2.18 mg/dL, and the eGFR level was 18.21±10.15 mL/min/1.73m^2. One month after biopsy, the average serum Cr level was 5.13±2.18 mg/dL, and the eGFR level was 15.80±11.84 mL/min/1.73m^2. One year after biopsy, the average serum Cr level was 6.41±3.11 mg/dL, and the eGFR level was 12.83±9.68 mL/min/1.73m^2.

The distribution of Banff lesion scores in kidney biopsies diagnosed with ca-ABMR is shown in Figure 1. Of the 14 patients, 7 were classified as high-risk based on their MVI score (ptc+g), and they exhibited significantly different survival outcomes compared to those in the low-risk group (p=0.03). In the high-risk group, the graft survival time was longer. No statistically significant difference in survival times was found between the low-risk (n=7) and high-risk (n=7) groups for the chronic tissue damage score (ci+ct+ti) (p=0.56). There was no statistically significant difference in graft survival times between the low-risk (n=7) and high-risk (n=7) groups for cg (p=0.31).

Immunohistochemical C4d staining was positive in all biopsies, diagnosed with ca-ABMR. C4d was detected as exhibiting linear positivity exclusively in peritubular capillaries in 21.43% of patients, in both peritubular capillaries and glomerular basement membranes in 28.57% of patients, and in peritubular capillaries, glomerular basement membranes, and interlobular arterioles in 50% of patients. In 86% of the biopsies, C4d staining scores were 2 or 3 in intensity.

Microscopic images of acute and chronic Banff lesions in biopsies of patients diagnosed with ca-ABMR are presented in Figure 2.

Table 1. Time-dependent variations in serum Cr and eGFR levels in renal transplant recipients with ca-ABMR

	Most recent level	Level at the time of biopsy	Level at the 1st month after biopsy	Level at the 1st year after biopsy
Serum Cr level (mg/dL)	1.80±0.77	4.37±2.18	5.13±2.18	6.41±3.11
eGFR level (mL/min/1.73m^2)	44±10.86	18.21±10.15	15.80±11.84	12.83±9.68

Cr: Creatinine, eGFR: Estimated glomerular filtration rate, ca-ABMR: Chronic active antibody-mediated rejection

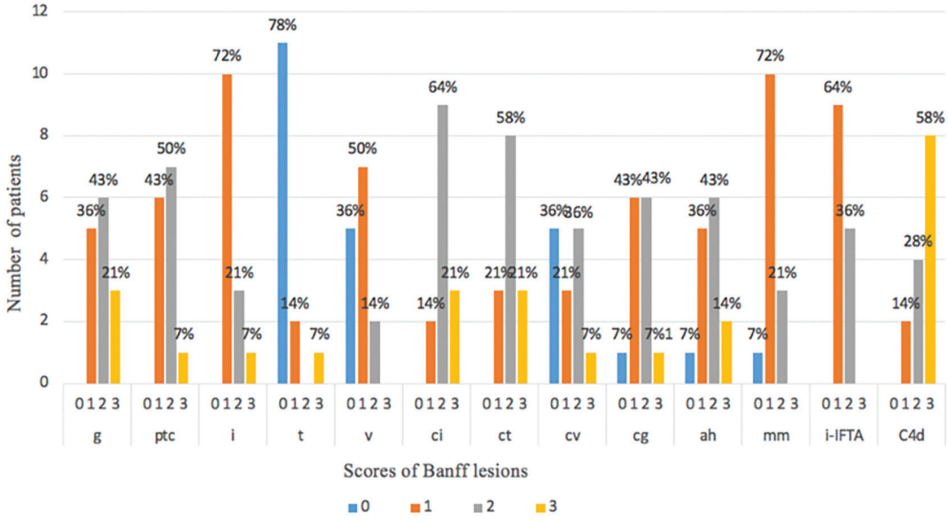

Figure 1. The distribution of Banff lesion scores in kidney biopsies diagnosed with ca-ABMR

ca-ABMR: Chronic active antibody-mediated rejection, g: Glomerulitis, ptc: Peritubular capillaritis, i: Interstitial inflammation, t: Tubulitis, v: Intimal arteritis, ci: Interstitial fibrosis, ct: Tubular atrophy, cv: Vascular intimal thickening, cg: Transplant glomerulopathy, ah: Arteriolar hyalinosis, mm: Mesangial matrix expansion, i-IFTA: Interstitial inflammation in areas of fibrosis and tubular atrophy, C4d: C4d staining score

The average follow-up time after transplantation was 93.64±52.14 months (range: 33-194 months). Following the pathological diagnosis, 10 patients (71.4%) received IVIg+plasmapheresis treatment, while 4 patients (28.6%) did not receive any treatment.

There was no statistically significant difference in MVI score (p=0.88), chronic tissue damage score (p=0.87), v (p=0.99), cg (p=0.99), or C4d score (p=0.50) between the treated and untreated groups.

There was no statistically significant difference in graft survival between the patients who received treatment (IVIg+plasmapheresis) and those who did not [p=0.94, log rank (Mantel-Cox) test]. The mean and median survival times in both treatment and non-treatment groups are presented in Table 2.

The average time from biopsy to graft loss was 58.50 months (range: 7-150 months). Graft loss was observed in 12 cases (85.7%). No statistically significant difference in age (p=0.95) or time from transplant to biopsy (p=0.99) was observed between the graft loss and non-graft loss groups. During the follow-up period, 3 patients (21.4%) died. The causes of death were coronavirus disease-2019 infection (n=2) and cardiovascular causes (n=1). The remaining 11 patients continue to live with hemodialysis.

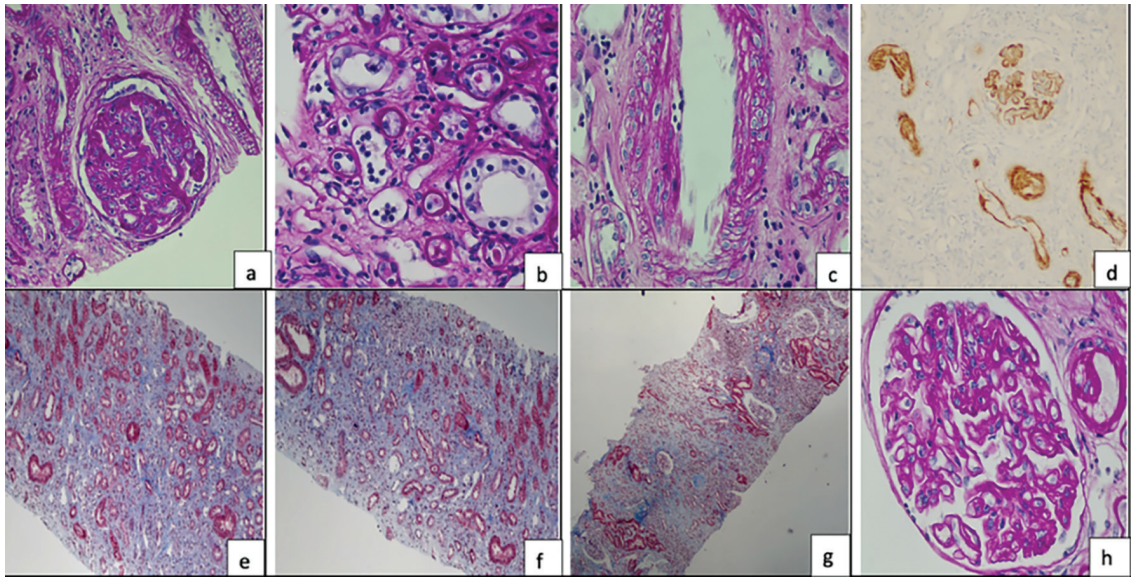

Figure 2. Acute (a,b,c,d) and chronic (e,f,g,h) Banff lesions in biopsies diagnosed with ca-ABMR

a: Glomerulitis (g) (PAS, x200), b: Peritubular capillaritis (pct) (PAS, x200) c: Intimal arteritis (v) (HE, x400) d: Positive C4d staining along the capillary basement membranes of glomeruli and in arterioles (C4d, x100), e: Interstitial fibrosis (ci) (Masson trichrome, x100) f: Tubular atrophy (ct) (Masson trichrome, x100), g: Total inflammation (ti) (Masson trichrome, x40), h: Transplant glomerulopathy (cg) (PAS, x400), ca-ABMR: Chronic active antibody-mediated rejection, PAS: Periodic acid-schiff, HE: Hematoxylin and eosin

Table 2. Mean and median survival times in treatment and non-treatment groups (month)

Treatment	Mean				Median			
	Estimate	Standard error	95% confidence interval		Estimate	Standard error	95% confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
Patients not receiving treatment	118.75	38.03	44.21	193.28	72	45.66	0	161.50
Patients receiving treatment (IVIg +PEX)	104.94	19.27	67.15	142.72	97	22.13	53.61	140.38
Overall	107.78	16.61	75.21	140.34	97	20.67	56.47	137.52

The log rank (Mantel-Cox) test was used

IVIg: Intravenous immunoglobulin, PEX: Plasma exchange

Discussion

The present study investigates the effects on graft survival of histopathological lesions, evaluated according to the Banff classification, in renal allograft biopsies diagnosed with ca-ABMR on graft survival. ca-ABMR is a major cause of long-term kidney transplant failure and is characterised by MVI, which is triggered by the binding of DSA to endothelial structures, and by fibrosis that develops as a result[3]. This process results in tissue damage to the allograft, precipitated by chronic inflammation, which in turn leads to loss of graft function. Histopathological monitoring of this process is important in terms of treatment response and prognosis.

In the present study, graft survival was found to be significantly prolonged in patients exhibiting elevated MVI scores (g+ptc) compared to those with low-risk scores. The distinct outcome observed in this study may be attributable to the earlier diagnosis and initiation of more intensive immunosuppressive therapy in patients with high MVI scores. Furthermore, the mean recipient age was found to be 40 years in the high-risk group and 45 years in the low-risk group. A potential explanation for this finding may be found in the enhanced immune response observed in younger recipients, even in the presence of MVI.

However, a substantial body of research has demonstrated that high MVI is frequently associated with an unfavorable prognosis[11-14]. The prototypic lesion of ABMR, MVI, has been shown to result from a broad range of mechanistic pathways within the renal allograft. This finding has been confirmed by both clinical and experimental studies. It is well established that antibodies that bind to non-self HLA molecules are capable of precipitating damage to graft endothelial cells. However, accumulating data indicate that various non-HLA autoantibodies and alloantibodies are also implicated in the injury cascade[15].

A new and distinct phenotype, referred to as isolated MVI (iMVI), has been incorporated into the most recent Banff classifications. This unique form is specifically defined by the presence of MVI without accompanying deposits of HLA DSA in the peritubular capillaries. This phenotype is associated with reduced T cell and natural killer cell infiltration in both the allograft and peripheral circulation. Moreover, the presence of only sparse plasma cell infiltration suggests an underlying injury mechanism different from that of antibody-mediated rejection. Graft survival in patients with iMVI has been reported to be longer compared to that in patients with ABMR[16-18]. Due to the inability to assess HLA DSA in all patients, it is possible that those with longer graft survival belong to a different immunologic phenotype.

Conversely, Banff scores (ci, ct, ti), which indicate chronic tissue damage, and cg scores did not demonstrate a significant relationship with graft survival. Although ci and ct have been reported to be associated with graft loss in the literature[10], this relationship was not found in the present sample. This phenomenon may be due to patients being observed predominantly in the late stage at the time of biopsy, and advanced fibrotic changes were no longer considered prognostic indicators.

ca-ABMR has been observed to occur in patients who have previously developed DSA or who have *de novo* DSA due to inadequate immunosuppression[3]. *De novo* DSA is regarded as a significant risk factor for the development of ca-ABMR[19]. Approximately 10% of low-risk kidney transplant recipients develop *de novo* DSA within the first five years after transplantation, with an increase continuing in subsequent years[20]. It is imperative to emphasise the significance of protocol biopsies, given the inability of our hospital to perform DSA analysis. Protocol biopsies represent an indispensable tool in the long-term monitoring of renal transplant recipients and have been established as playing a pivotal role, especially in immunologically high-risk patients with previous DSA[21].

It has been suggested that the presence of DSA may trigger humoral rejection via complement activation, which could lead to tissue damage and coagulation. Furthermore, complement activation has been demonstrated to promote the migration of inflammatory cells via the innate immune response, which in turn causes endothelial damage. It may this inflammatory response may result in persistent g and ptc[22]. cg, severe EM-documented ptcml stratification, or unexplained new arterial intimal fibrosis is recognized associations of chronic tissue damage development[23].

Immunohistochemical C4d staining was positive in all cases, thus reinforcing its diagnostic utility for ca-ABMR. It is noteworthy that linear C4d accumulation was observed in peritubular capillaries, glomerular basement membranes, and interlobular arterioles. The significance of glomerular C4d (gC4d) accumulation remains a subject of debate. However, studies by Lee et al.[24] and Shimizu et al.[25] have demonstrated a strong correlation between gC4d and markers of antibody-mediated damage, including ptc, g, and cg. A further study indicated that gC4d could be a more reliable marker for ca-ABMR than peritubular C4d[26]. The findings of this study are consistent with the conclusions of

the aforementioned reports, which indicate that glomerular and arteriolar C4d positivity is frequently detected.

The initial treatment for active ABMR is usually plasma exchange (PEX) and IVIg or combinations of PEX, IVIg and steroids[27]. However, according to the extant literature, although histological improvement is achieved with combinations of IVig, PEX and rituximab in ca-ABMR patients, its impact on long-term allograft survival remains limited[28,29]. Current studies demonstrate that the administration of bortezomib, eculizumab, rituximab, PEX, and their combinations has not yielded a convincing benefit in kidney recipients diagnosed with ca-ABMR[6]. The heterogeneity of treatment methods and the variation in the histopathological features of patients complicate the evaluation of treatment efficacy[23]. Currently, there is no proven effective treatment for ca-ABMR. The present study lends further support to these findings. No significant difference was found in terms of graft survival between patients who received treatment and those who did not.

Study Limitations

In selecting patients who received treatment, the main criteria included the diagnosis of ca-ABMR, positive C4d staining, (particularly in ptc and glomerular basement membrane), a C4d score of ≥2 according to the Banff classification, the presence of proteinuria, and/or deterioration in graft function. However, treatment decisions were made by different clinicians within the same center, which introduced a degree of heterogeneity in therapeutic approaches. This constitutes a significant limitation of the study. Additionally, the patients who did not receive treatment exhibited similar histopathological findings but were managed conservatively due to stable clinical status or differences in clinical judgment.

The high-MVI group exhibited a significantly prolonged survival duration, an unexpected finding that may be attributable to several factors. This phenomenon could be attributed to lead-time bias, as high-MVI patients were frequently subjected to biopsies at earlier stages, while low-MVI cases exhibited more chronic injury. Furthermore, the intensity of treatment may have been a contributing factor, as high-MVI findings often result in more intensive therapy and enhanced monitoring. The findings might also be influenced by the heterogeneity in low MVI, since substantial chronic damage within this group has still been shown to predict poor outcomes. Finally, unmeasured immunologic factors, such as incomplete DSA data, could have affected the results. In summary, while this study suggests that MVI may have prognostic value in ca-ABMR, the findings must be interpreted with caution owing to the small cohort, lack of DSA, and treatment heterogeneity. The prognostic value of histopathological parameters should be re-evaluated in larger, prospective, DSA-followed cohorts.

Conclusion

The identification of predictors of treatment response in patients with ca-ABMR remains a significant clinical challenge. The results of the current study underscore the limited impact of currently available therapies on graft survival and emphasise the necessity for prospective studies with larger cohorts and novel biomarkers. The development of innovative therapeutic strategies and standardised monitoring protocols, including protocol biopsies and DSA surveillance, may facilitate earlier diagnosis and enable tailored interventions. According to this study, the majority of patients exhibited advanced graft dysfunction and late-stage histological changes, which limited the potential for therapeutic response. It is recommended that future research place a priority on the early detection and risk stratification of ca-ABMR, with a view to improving long-term outcomes.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (approval number: 16/16, date: 24.10.2024).

Informed Consent: Informed consent was waived by the institutional review board due to the retrospective nature of the study.

Footnotes

This study was presented as an oral presentation at the 15th Congress of the Turkish Transplantation Centers Coordination Association (October 17-20, 2024, Gaziantep).

Authorship Contributions

Surgical and Medical Practises: A.A., Concept: A.A., Design: A.İ., Ü.Y., Data Collection or Processing: S.G., Analysis or Interpretation: Ü.Y., Literature Search: S.G., Writing: Ş.Y., A.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

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