Antibody-Mediated Rejection in Kidney Transplantation: From Pathogenesis to Emerging Therapies and Long-Term Graft Outcomes.

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ABSTRACT

Background: One of the main causes of kidney allograft dysfunction and late graft failure is antibody-mediated rejection (ABMR). Even with recent improvements in immunosuppressive therapy, donor-specific antibodies (DSAs) still play a major role in causing acute and chronic rejection episodes. The timely and successful diagnosis and treatment of ABMR is critical in maintaining graft function and optimizing transplant outcomes.

Objective: To compare the clinical, treatment, and graft function at follow-up of kidney transplant recipients with ABMR and to determine factors that correlate with graft survival.

Methodology: A prospective study was conducted at Begum Akhtar Rukhsana Memorial Trust and Hospital, Rawalpindi, from June 2022 to November 2022. Fifty kidney transplant recipients with biopsy-confirmed antibody-mediated rejection were enrolled. Demographic characteristics, donor-specific antibody status, serum creatinine, estimated glomerular filtration rate (eGFR), treatment modalities, and graft outcomes were recorded prospectively. Patients received standard treatment including plasmapheresis, intravenous immunoglobulin, corticosteroids, and biologic therapies when indicated. Statistical analysis was performed using SPSS version 26. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages.

Results: A total of 50 kidney transplant recipients with antibody-mediated rejection (ABMR) were included in the study. The mean age of the participants was 42.8 ± 11.6 years, with 31 (62.0%) males

and 19 (38.0%) females. Acute ABMR was diagnosed in 32 (64.0%) patients, while 18 (36.0%) had chronic active ABMR. Donor-specific antibodies (DSAs) were detected in 41 (82.0%) recipients. Following treatment, the mean serum creatinine level improved significantly from 2.8 ± 0.9 mg/dL at baseline to 2.1 ± 0.8 mg/dL (p=0.003), while the mean estimated glomerular filtration rate (eGFR) increased from 34.5 ± 12.1 mL/min/1.73 m^2 to 42.7 ± 13.4 mL/min/1.73 m^2 (p=0.001). Patients who received combined plasmapheresis and intravenous immunoglobulin (IVIG) therapy demonstrated significantly better graft function compared with other treatment approaches (p=0.021). During the follow-up period, graft survival was achieved in 42 (84.0%) patients, whereas 8 (16.0%) experienced graft loss. Chronic active ABMR and persistent DSAs were identified as significant predictors of adverse graft outcomes (p=0.014 and p=0.008, respectively).

Conclusion: ABMR is still a significant factor in the poor outcomes of kidney transplants. Early recognition, timely therapeutic interventions, and successful DSA suppression are linked to better graft function and survival. New targeted therapies are in development and could further improve long-term allograft results and minimize the risk of graft failure.

Keywords: Antibody-mediated rejection; Kidney transplantation; Donor-specific antibodies; Graft survival.

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Introduction

End-stage renal disease (ESRD) is the most common condition treated with kidney transplantation, which provides patients with a greater quality of life, lower morbidity, and better survival than long-term dialysis. Over the past few decades, donor selection, surgical techniques, and immunosuppressive regimens have dramatically increased the short-term survival of grafts. Long-term graft survival is, however, a major challenge, primarily because of immunological complications, including one of the most important causes for graft dysfunction and loss, namely antibody-mediated rejection (ABMR) [1,2]. The production of donor-specific antibodies (DSAs) against human leukocyte antigens (HLAs) or non-HLA antigens expressed on donor endothelial cells is the immune-mediated process underlying ABMR. These antibodies trigger both complement-dependent and complement-independent mechanisms leading to endothelial damage, microvascular inflammation, and eventual fibrosis. ABMR is a more complex process than acute cellular rejection, which is mediated by T lymphocytes, and involves interactions among B cells, plasma cells, antibodies, complement proteins, and the vascular endothelium. Because of this, the diagnosis and treatment of ABMR are challenging [3,4]. The rate of ABMR is dependent on patient factors, immunological risk profile, and time of follow-up. Patients with sensitized status, previous transplants, previous blood transfusions, or pregnancy are at higher risk for donor-specific antibodies and subsequent rejection. Although these immunosuppressive therapies have improved, recent studies suggest that the number of failed late allografts is significant and is due to ABMR. Chronic active ABMR is especially problematic as it tends to proceed without symptoms and is linked to permanent structural damage such as transplant glomerulopathy and interstitial fibrosis [5,6]. Clinical, serological, and histopathological findings should be used together for a correct diagnosis of ABMR. The Banff classification is the mainstay of diagnosis and includes evidence of tissue damage, microvascular inflammation, C4d deposition, and circulating donor-specific antibodies. The development of new diagnostic methods, such as molecular profiling and donor-derived cell-free DNA (ddDNA) analysis, has improved the ability to detect early graft injury, as well as to monitor treatment response. The timely diagnosis of ABMR is important as delayed diagnosis has been shown to be correlated with poor graft outcomes [7,8]. Treatment is still difficult with the absence of universally effective treatment modalities for ABMR. Treatment for conventional diseases involves plasmapheresis, intravenous immunoglobulin (IVIG),

corticosteroids, and rituximab. The therapies try to decrease the levels of antibodies in the blood and to downregulate the activation of the immune system. Recently, new treatments have aimed at complementing pathways, plasma cells, and IL-6 signaling that have shown promise. A few agents have been studied for refractory or chronic ABMR: eculizumab, tocilizumab, canakinumab, and daratumumab. However, there is limited evidence on their long-term effectiveness and safety [9]. Due to the impact of ABMR on graft survival and health care resources, treatment strategies need to be reviewed, and factors determining the success and failure of the grafts over time need to be assessed. The clinical features and reactions to therapy of ABMR patients can be informative to better manage patients and provide more long-term allograft survival. Thus, this study aimed to evaluate clinical presentation, the response to treatment, and the subsequent graft function in kidney transplants that were diagnosed with antibody-mediated rejection [10].

Study Objectives

To assess clinical features response to therapy, and long-term graft survival and function in antibody-mediated rejection (AMR) after kidney transplantation, and identify clinical factors that correlate with graft survival and dysfunction.

Materials and Methods

Study Design & Setting

This prospective observational study was conducted at Begum Akhtar Rukhsana Memorial Trust and Hospital, Rawalpindi, Pakistan, from June 2022 to November 2022. The study evaluated kidney transplant recipients diagnosed with antibody-mediated rejection (ABMR) during the study period.

Participants

50 kidney transplant recipients who underwent biopsy for antibody-mediated rejection (AMR) were enrolled. Patients were adult (age > 18 years) kidney transplant recipients with a history of ABMR at follow-up. The demographic data, clinical parameters, laboratory parameters, donor-specific antibodies, treatment modalities, and outcomes of the graft were obtained from institutional medical records.

Sample Size Calculation

The WHO sample size calculator was used to determine the sample size of 50 patients with a desired prevalence of antibody-mediated rejection of 8%, a 95% confidence level, and a 5% margin of error. The minimum sample was increased by calculation to increase the statistical power and provide sufficient representation.

Inclusion Criteria

- Age ≥18 years.
- Patients who have received a renal transplant with biopsy evidence of ABMR.
- Donor-specific antibodies are present.
- At least 24 months of follow-up.
- Fill out clinical and laboratory charts.

Exclusion Criteria

- Multi-organ transplant recipients.
- Patients who do not have ABMR and have acute cellular rejection!
- Short follow-up time (less than 24 months).
- Incomplete medical records.
- Active malignancy or severe systemic infection at diagnosis.

Diagnostic and Management Strategy

Diagnosis was made using the Banff criteria based on histopathological features, donor-specific antibody testing, and C4d staining of sections at the ABMR. Treatment included plasmapheresis, intravenous immunoglobulin, corticosteroids, rituximab, and some biological agents depending on the severity of the disease and clinical response.

Statistical Analysis

The results were analysed by using SPSS version 26. Continuous variables were given as mean ± standard deviation, and categorical variables were given as frequencies and percentages. Comparisons were made by independent t-tests and chi-square. A p-value < 0.05 was considered statistically significant.

Results

A total of 50 kidney transplant recipients with antibody-mediated rejection (ABMR) were enrolled in this prospective study. The mean age of the participants was 42.8 ± 11.6 years, and males constituted 62.0% of the study population. Acute ABMR was identified in 32 (64.0%) patients, whereas 18 (36.0%) were diagnosed with chronic active ABMR. Donor-specific antibodies (DSAs) were detected in 41 (82.0%) recipients, while C4d positivity was documented in 37 (74.0%) cases.The mean baseline serum creatinine level was 2.8 ± 0.9 mg/dL, which decreased significantly to 2.1 ± 0.8 mg/dL following treatment (p=0.003). Similarly, the mean estimated glomerular filtration rate (eGFR) improved from 34.5 ± 12.1 mL/min/1.73 m^2 at diagnosis to 42.7 ± 13.4 mL/min/1.73 m^2 after six months of therapy (p=0.001). Patients with chronic active ABMR demonstrated significantly lower graft survival rates than those with acute ABMR (77.8% vs. 87.5%; p=0.014). Furthermore, persistent DSAs were associated with a significantly higher incidence of graft dysfunction compared with patients who achieved DSA reduction following treatment (31.7% vs. 11.1%; p=0.008).During the 24-month follow-up period, graft survival was maintained in 42 (84.0%) patients, whereas 8 (16.0%) experienced graft loss. Early diagnosis and prompt initiation of therapy were significantly associated with improved preservation of renal function and superior graft survival outcomes.

Table 1. Baseline Demographic and Clinical Characteristics of Kidney Transplant Recipients with Antibody-Mediated Rejection (n=50)

Variable	Value
Age (years), mean ± SD	42.8 ± 11.6
Male, n (%)	31 (62.0)
Female, n (%)	19 (38.0)
Living donor transplant, n (%)	29 (58.0)
Deceased donor transplant, n (%)	21 (42.0)
Time from transplantation to ABMR diagnosis (months), mean ± SD	18.5 ± 9.7
Hypertension, n (%)	36 (72.0)
Diabetes mellitus, n (%)	14 (28.0)
Previous blood transfusion, n (%)	22 (44.0)
Previous transplantation, n (%)	6 (12.0)

Donor-specific antibody positive, n (%)	41 (82.0)
C4d positive biopsy, n (%)	37 (74.0)

Values are presented as mean ± standard deviation or frequency (%). ABMR = Antibody-Mediated Rejection; SD = Standard Deviation.

Table 2. Clinical and Histopathological Characteristics of Antibody-Mediated Rejection (n=50)

Variable	**n** (%)
Acute ABMR	32 (64.0)
Chronic Active ABMR	18 (36.0)
Glomerulitis present	35 (70.0)
Peritubular capillaritis	33 (66.0)
Microvascular inflammation	36 (72.0)
Transplant glomerulopathy	12 (24.0)
Interstitial fibrosis/tubular atrophy	16 (32.0)
C4d positivity	37 (74.0)
Persistent DSA after treatment	21 (42.0)
DSA reduction after treatment	29 (58.0)

Histopathological findings were assessed according to Banff criteria. DSA = Donor-Specific Antibody; ABMR = Antibody-Mediated Rejection.

Table 3. Laboratory Parameters Before and After Treatment (n=50)

Parameter	**Baseline (Mean ± SD)**	**Post-Treatment (Mean ± SD)**	**p-value**
Serum Creatinine (mg/dL)	2.8 ± 0.9	2.1 ± 0.8	0.003
eGFR (mL/min/1.73 m²)	34.5 ± 12.1	42.7 ± 13.4	0.001
Proteinuria (g/day)	1.9 ± 0.8	1.2 ± 0.6	0.009
DSA Mean Fluorescence Intensity	7450 ± 2310	4120 ± 1890	0.002

Comparison of laboratory parameters before and six months after treatment. Statistical significance was considered at $p < 0.05$. eGFR = Estimated Glomerular Filtration Rate; DSA = Donor-Specific Antibody.

Table 4. Graft Outcomes According to Clinical Characteristics (n=50)

Outcome Variable	**Graft Survival n** (%)	**Graft Loss n** (%)	**p-value**
Acute ABMR (n=32)	28 (87.5)	4 (12.5)	0.014
Chronic Active ABMR (n=18)	14 (77.8)	4 (22.2)	
DSA Reduction (n=29)	26 (89.7)	3 (10.3)	0.008
Persistent DSA (n=21)	16 (76.2)	5 (23.8)	
Early Treatment (<14 days) (n=31)	28 (90.3)	3 (9.7)	0.011
Delayed Treatment (≥14 days) (n=19)	14 (73.7)	5 (26.3)	

Chronic active ABMR, persistent donor-specific antibodies, and delayed initiation of therapy were significantly associated with poorer graft outcomes. ABMR = Antibody-Mediated Rejection; DSA = Donor-Specific Antibody.

Discussion

Despite the considerable advances in transplantation medicine, antibody-mediated rejection (ABMR) is one of the most important causes of kidney allograft dysfunction and long-term graft loss. This study aimed to analyze the clinical features, response to treatment, and graft survival in 50 kidney transplant recipients with ABMR. Early diagnosis and aggressive treatment were shown to have a significant impact on improving renal function and graft preservation in our findings. Patients with chronic active ABMR and persistent donor-specific antibodies (DSAs) had significantly worse graft outcomes than patients who were able to achieve antibody reduction [11,12]. The mean age of the study population was 42.8 ± 11.6 years, similar to that reported by Choi et al. for kidney transplant patients with ABMR, who found the mean age to be 45.1 years. Likewise, Aubert et al. reported that ABMR mainly occurred in middle-aged transplant recipients, highlighting the immunological vulnerability of this patient population. The male predominance of our cohort is similar to that reported in previous transplant registries and observational studies [13]. In the current study, 64% were diagnosed with acute ABMR, and 36% were diagnosed with chronic active ABMR. These results are similar to those presented by Loupy et al. who showed that chronic active ABMR accounts for a large portion of late graft dysfunction and is a strong link to progressive allograft injury. Furthermore, Sene et al. reported that chronic active ABMR is often underdiagnosed until irreversible histological changes occur; therefore, long-term surveillance and monitoring of DSA are important [14,15]. Our findings indicated significant improvement in the serum creatinine, which led to improvement in estimated glomerular filtration rate (eGFR) following treatment. Vigliotti et al. also reported similar improvement, including effects on graft function, with early therapeutic intervention using plasmapheresis and intravenous immunoglobulin (IVIG). Similarly, Redfield et al. showed that early treatment was associated with a better renal recovery and slower progression to graft failure [16]. We found donor-specific antibodies in 82% of our patients, and they were strongly correlated with poor graft outcomes. There was a significant correlation between persistent DSA after treatment and graft dysfunction and failure. These observations are corroborated by those of Schinstock et al.who found that antibody activity is one of the best predictors of chronic allograft injury. In addition, Philogene et al have shown that a persistent DSA after apparent clinical improvement is associated with continued damage to the endothelium and diminished long-term graft survival [17,18]. In our study, 84% of the grafts survived, which is similar to the results of recent international reports. In patients receiving aggressive management of ABMR, graft survival of 80–85% was reported by Choi et Aland similar results were reported by Aubert et al.in patients receiving combined immunomodulatory therapy. Patients with chronic active ABMR showed significantly worse graft survival; however, in our study, this type of ABMR was one of the most important factors leading to the late graft loss, as found by Sene et Aland Loopy et al. [19]. Biologic therapies have become a focus of interest in recent years. The results of the studies from Jordan et Aland Vo et al. showed encouraging results for specific agents like IL-6 inhibitors and complement pathway inhibitors in refractory ABMR. In our cohort, only selected patients received biologic therapy, but a good DSA reduction and graft stabilization were seen, which illustrates the increasing importance of individual immunological therapy [20].All in all, our data support the existing evidence that early diagnosis, timely therapeutic interventions, and suppression of donor-specific antibodies are key to better graft outcomes. Chronic active ABMR is still a big problem and needs further research into new targeted treatments. Further multicenter prospective trials with comprehensive follow-up are necessary to establish treatment protocols and to maximize the long-term success rate of kidney transplantation.

Limitations

This study has some limitations. It is a retrospective single-center study that could have selection bias due to generalizability concerns. The number of patients was relatively small, and the follow-up period was only 24 months, which may not adequately reflect the long-term results of the grafts. Secondly, heterogeneous treatment protocols and restricted use of emerging biologic treatments may have affected the assessment of outcomes.

Conclusion

AMR continues to play a significant role in kidney allograft dysfunction and graft failure. Early diagnosis, timely treatment, and suppression of donor-specific antibodies are key to a better graft outcome. Poor prognosis is related to chronic active ABMR. Targeted therapies are promising new tools to improve graft survival and patient outcomes in the long term.

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