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Histopathological diagnoses revealed by indication-based renal allograft biopsies: a retrospective analysis

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ABSTRACT

Objectives: Although there have been several advances in post-solid organ transplantation immunosuppression medications over the last two decades, the long-term survival of renal allografts did not significantly improve. Renal allograft biopsy is a helpful tool for determining the cause of graft dysfunction and adjusting patient management.

Methods: Patients who received kidney transplantation and underwent allograft biopsy in Istinye University Hospital between January 2017 and January 2023 constituted the target population of this study. Demographic parameters, clinical data and biopsy indications, and histopathological assessment results of the patients were retrospectively analyzed.

Results: Overall, 74 patients were included. The histopathology results included acute T-Cell mediated rejection (TCMR) (n = 15, 20%), tubular atrophy/chronic allograft nephropathy (IFTA) (n = 11, 15%), calcineurin inhibitor (CNI) toxicity (n = 2, 3%), chronic antibody-mediated rejection (ABMR) (n = 2, 3%), borderline pathology (n = 10, 13.5%), normal histology (n = 5, 6.5%), transplant glomerulopathy (TG) (n = 5, 6.5%), acute ABMR (n = 4, 5%), acute tubular necrosis (n = 7, 9%), polyomavirus nephropathy (n = 3, 4%) and non-specific changes (n = 10, 13.5%). The C4d was positive in 12% (n = 9) of the graft biopsies. In 73% (n = 54) of cases, the treatment strategy was changed based on biopsy results. Among all patients, 19 (25.6%) lost their grafts during follow-up.

Conclusions: According to the histopathological analysis results, acute TCMR, IFTA, and borderline pathology were the most common causes of renal graft dysfunction. Renal allograft biopsy led to a remarkable change in treatment strategies in a significant number of cases.

Keywords: Renal, allograft, biopsy, histopathology, diagnosis

Renal transplantation (RT) is the optimal treatment for end-stage kidney disease (ESRD) [1]. Although the advances in surgical techniques and immunosuppression (IS) protocols led to a significant increase in graft survival rates during the last two decades, renal allograft biopsy still has a significant

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role in patient management, particularly in the setting of graft dysfunction [2].

It is known that a broad spectrum of clinical entities can lead to graft damage [3]. In clinical practice, indication biopsies are performed after every attempt is made to diagnose or exclude all potential causes of renal allograft dysfunction such as hypovolemia, drug interactions leading to an increase in the trough calcineurin levels, vascular or urological problems including arterial stenosis, ureteral stricture, lower urinary tract obstruction or systemic infections or recurrence of the primary kidney disease [4]. On the one hand, it is known that renal allograft biopsy is not exempt from potential complications such as bleeding, hematoma or urinoma formation, infections, and graft loss; thus, it is considered the last resort in the diagnostic management of RT patients [5]. On the other hand, delaying or ignoring renal allograft biopsy can lead to irreversible outcomes [5]. In order to prevent permanent damage to the graft, the treatment strategies can be tailored according to the biopsy result, and the longevity of the graft function can be saved. Therefore, transplant practitioners need to know the impact of their "indication biopsy" strategy on their approaches regarding patient treatment.

This study was performed to analyze the renal allograft biopsy results and determine the impact of indication biopsies on treatment strategies at our transplant center.

METHODS

This study was designed as a retrospective single-center study. After obtaining approval from the Ethical Review Committee of Istinye University Hospital (Date:12.04.2023, Decision No.: 23/102), data of the patients who received kidney transplantation and underwent a conclusive renal allograft biopsy at our center between January 2017 and January 2023 were reviewed. All patients consented to the use of their medical data for research purposes.

The initial retrospective review revealed 84 patients. Among those, 6 were excluded since they underwent renal transplantation at another center, while 2 were not included due to patients with incomplete follow-up data. In addition, 2 patients with inconclusive biopsies were omitted. Thus, 74 patients were included in this study. The inconclusive biopsies repeated for obtaining a conclusive biopsy specimen according to the Banff criteria were also omitted [6]. All renal allograft biopsies were performed on a specific indication. No protocol biopsies were performed.

Data including demographic parameters (i.e., age and gender), donor age, the primary reason for ESRD, type of donor (i.e., deceased donor, live-related or live-unrelated), the time between RT and renal allograft biopsy, indication for biopsy, major histocompatibility complex antibody (anti-MHC) and C4d status, histopathological diagnosis, shift in treatment strategy after obtaining the biopsy result and duration of follow-up after renal allograft biopsy were retrieved from electronic patient folders. All renal allograft biopsy specimens were analyzed by the same pathologist experienced in this field. The pathologist based the assessments on the Banff 2007 classification [6]. The retrieved data were transferred to an electronic database for statistical analysis.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS v23, IBM, Armonk, NY, US) software. The data were analyzed using descriptive statistics. Frequencies, percentages, and means were presented where appropriate.

RESULTS

The histopathological diagnoses revealed by 74 renal allograft biopsies were included in the study. Three

Table 1. Primary diseases of the patients

Primary disease	n (%)
Diabetes mellitus	16 (21.5)
Hypertension	13 (17.5)
IgA nephropathy	3 (4)
Focal sclerosing glomerulonephritis	3 (4)
Reflux nephropathy	2 (2.5)
Nephronophthisis	2 (2.5)
Obstructive uropathy	2 (2.5)
Unknown	9 (12)
Other	24 (33.5)

Table 2. Renal allograft biopsy indications

Indication	n (%)
Increased serum creatinine level	60 (81)
Proteinuria	7 (9)
Increased serum creatinine level and proteinuria	2 (3)
Delayed graft function	5 (7)

(4%) of the biopsy specimens were obtained by repeat biopsies since the initial intervention failed to provide an "adequate" specimen for a satisfactory histopathological assessment. Patients were aged between 3 and 67, and the mean patient age was 3.4 years. Among these patients, 58 (78.4%) were male, and 16 (21.6%) were female. Live-related, live-unrelated, and deceased donors were the donor types in 58 (78.4%), 10 (13.5%), and 6 (8.1%), respectively. The mean donor age was 44.5 years (range: 21-68 years). The mean duration between RT and renal allograft biopsy was 217 day (range: 8-1680 days). The primary diseases leading to end-stage renal disease are listed in Table 1.

The renal graft biopsy indications are displayed in Table 2. An increase in serum creatinine level was the most common indication (81%) for biopsy. The histopathological diagnoses are listed in Table 3. Analysis of the histopathological assessment reports revealed that acute T cell-mediated rejection (TCMR) was the most frequent (20%) diagnosis. The shifts in the treatment strategies based on renal allograft biopsy results are displayed in Table 4.

This analysis revealed that biopsy results led to a significant change in treatment in 73% (n = 54) of the patients. The mean duration of follow-up after renal allograft biopsy was 30.5 [1-60] months. None of the patients died during the study period; however, 25.5% (n = 19) of grafts failed. Among these 19 grafts, 8 were diagnosed with acute rejection, 3 had transplant glomerulopathy (TG), and 2 had interstitial fibrosis and tubular atrophy (IFTA).

Table 3. Histopathological diagnoses of the patients

Diagnosis	n (%)
Acute T-cell mediated rejection	15 (20)
Acute antibody-mediated rejection	4 (5)
Interstitial fibrosis and tubular atrophy	11 (15)
Chronic antibody-mediated rejection	2 (3)
Calcineurin inhibitor toxicity	2 (3)
Borderline pathology	10 (13.5)
Acute tubular necrosis	7 (9)
BK virus nephropathy	3 (4)
Non-specific changes	10 (13.5)
Normal histology	5 (7)
Transplant glomerulopathy	5 (7)

DISCUSSION

Since renal allograft biopsy is an invasive intervention with potential complications endangering the survival of the graft or the recipient, it is challenging for clinicians to proceed with this procedure during the follow-up of kidney transplant recipients [7, 8]. On the other hand, while some centers, like ours, perform on-indication biopsies only, others perform protocol biopsies and, therefore, have a heterogeneous renal allograft biopsy specimen pool. We conducted our study with the belief that a retrospective review of our on-indication biopsy renal allograft biopsy data and analyzing their positive impact on patent management could encourage transplant practitioners during the decision-making processes for on-indication biopsies.

It is known that renal allograft biopsy is the technique of choice for diagnosing rejection and other potential causes of graft dysfunction [7]. Although some centers perform periodic protocol biopsies, most kidney transplant centers suggest allograft biopsies on

Table 4. Changes in treatment strategies based on graft biopsy results

Shift in treatment strategy	n (%)
Plasmapheresis	4 (5.5)
Pulse steroid treatment	30 (40.5)
Follow-up	20 (27)
Intravenous hydration	7 (9.5)
Reduction in immunosuppression	3 (4)
Other	10 (13.5)

specific indications [8]. The main reason for this approach is that rejection may lead to adverse outcomes regarding the survival of the graft, especially if it remains undiagnosed or diagnosed late [9]. In our study, most renal transplant biopsies were performed due to increased serum creatinine levels, and the biopsies led to a significant shift in patient management in 73% of the cases. This finding highlights the importance of performing renal allograft biopsy for early diagnosis and tailoring the patient management protocols.

McDonald *et al*. [10] worked on the impact of acute TCMR and renal transplant outcomes. These authors analyzed the data of 4325 renal transplant recipients and concluded that acute rejection increased the risk of graft loss [10]. In our study, 25% of the cases were diagnosed with acute rejection. While the patients with acute TCMR were managed with pulse steroids and increasing the dose of maintenance IS, those with acute antibody-mediated rejection (ABMR) were mainly treated by plasmapheresis.

In consistency with acute rejection, chronic rejection was also reported to be related to graft failure. It is known that chronic ABMR is characterized by C4d deposits in peritubular capillaries, transplant glomerulopathy, peritubular capillary basement membrane layering, and intimal fibrous thickening [10]. Based on these criteria, chronic ABMR was diagnosed in 3% of the cases in our study.

Parajuli *et al*. [11] analyzed the histopathological characteristics of the renal allograft biopsy specimens and the reasons for renal graft failure in a cohort including 329 patients with graft failure. These authors noted that the three most common causes of graft failure were acute rejection (40%), TG (17%), and IFTA (13%)- the distribution of the reasons for graft failure in our cohort aligned with these data.

In 2023, Afrakoti *et al*. [12] reported the histopathological findings of their patients with renal allograft dysfunction. They worked on the data from 300 renal allograft biopsies and concluded that acute TCMR, IFTA, and calcineurin inhibitor (CNI) toxicity were the most common causes of allograft dysfunction in their cohort. In line with these data, the most frequent histopathological diagnosis was acute TCMR in our cohort. Afrakoti *et al*. [12] stated that indication biopsies were beneficial in selecting the optimal treatment plans for preventing permanent graft failure. Our results led to a similar conclusion.

Our review revealed that 3 (4%) patients were diagnosed with polyomavirus (i.e., BK virus) infection. Although this rate is relatively low, it is known that BK virus infection might affect allograft survival. Hogan *et al*. [13] noted that the BK virus had a significant role in allograft failure. In line with this finding, Sharma *et al*. [14] reported that early detection of BK-related nephropathy was beneficial for preventing early graft loss. In our cohort, timely diagnosis of BK virus nephropathy led to the timely modification of the IS regimens and prevention of graft loss in all cases with BK virus infection.

In compliance with BK nephropathy, timely diagnosis and treatment of rejection is also crucial in preventing graft loss [15]. Since acute rejection necessitates initiating anti-rejection treatments with potential adverse effects, including increased risk of opportunistic infections and development of malignant disorders, correct diagnosis of this clinical entity is critical [16]. According to the Banff criteria, the pathologist should evaluate the specimen adequacy as the first step of the histopathological assessment of the renal allograft biopsy specimens [6]. Cimen *et al*. [17] worked on the impact of specimen adequacy in the histopathological interpretation of the renal allograft biopsy specimens and the interobserver variations between the pathologists. These authors stated that the interobserver variation significantly increased in the setting of unsatisfactory biopsy specimens. In line with this conclusion, the "minimal" or "unsatisfactory" specimens were not used for histopathological diagnosis in our cohort, and these biopsies were repeated.

Limitations

Our study has some limitations that must be considered while evaluating its findings. First, it is a single-center, retrospective study with a small sample. Second, the follow-up duration is short. Finally, all biopsy specimens were evaluated by a single pathologist, and there was no chance to analyze the validity of the data by assessing the interobserver variation.

CONCLUSION

We conclude that a timely-performed, conclusive indication biopsy is valuable in diagnosing the reasons for renal allograft dysfunction. This approach can sig-

nificantly change patient management and contribute to all endeavors to prevent graft loss.

Authors' Contribution

Study Conception: EE, MT; Study Design: AA, TŞ; Supervision: AD; Funding: N/A; Materials: N/A; Data Collection and/or Processing: HBU, SA; Statistical Analysis and/or Data Interpretation: EE, MT; Literature Review: EE, AD; Manuscript Preparation: EE, TŞ and Critical Review: HBU, AD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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