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Original Paper

CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS OF BIOPSY-PROVEN KIDNEY GRAFT REJECTION IN LATVIA

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*Kidney transplantation has become a preferred treatment for many patients with end-stage renal disease, leading to increased quality of life. In recent decades, results in kidney transplantation have been improving, but allograft rejection remains an important clinical problem. This retrospective study reviewed all kidney allograft biopsies performed at Pauls Stradiņš Clinical University Hospital from January 2014 to December 2022, with the aim to determine clinical and histopathological characteristics, treatment, and short-term outcomes of biopsy-proven kidney graft rejection in Latvia. Rejection was diagnosed according to clinical, laboratory, and biopsy-proven acute rejection histological criteria; classified and subdivided using Banff criteria (a total five groups). Treatment strategies, laboratory data at the time of biopsy and after one-year follow-up were analysed. A total of 153 allograft biopsies were included. The majority of the grafts were from deceased donors. Besides augmented maintenance immunosuppression for almost all patients, pulse steroids were the most administered treatment, followed by plasma exchange, rituximab, immunoglobulins, and anti-thymocyte globulin in different, mainly non-homogenous combinations. Acute antibody-mediated rejection was diagnosed most often. The most favourable outcomes considering allograft function were in the acute cellular rejection group after one-year treatment compared to the worst outcome chronic-active antibody mediated rejection (caAMR) group (*p = *0.03). Furthermore, the caAMR group had the highest number of patients who returned to dialysis or died after one year.*

Keywords: *kidney transplantation, rejection, acute and chronic allograft failure.*

INTRODUCTION

For the past decades, kidney transplantation has become a preferred treatment for many patients with end-stage renal disease, leading to increased quality of life and survival compared to patients on dialysis (Wolfe *et al*., 1999; Eckardt *et al.*, 2009; Tonelli *et al.,* 2011; Poggio *et al.,* 2021). In recent years, results in kidney transplantation have been improving due to advances in surgical techniques and immunosuppressive therapy, but allograft rejection remains an important clinical problem (Lentine *et al.,* 2024). Patients with acute kidney transplant rejection are at increased risk of developing chronic allograft changes and resulting in poor long-term patient and allograft outcomes. Furthermore, rejection reactions are an independent risk factor for long-term survival of transplanted kidneys (Clayton *et al.,* 2019).

Kidney transplant dysfunction with either changes in laboratory parameters or clinical suspicion might be caused by many reasons. An allograft biopsy should be performed, as it is the gold standard for assessing the status of kidney transplant, and when used in conjunction with Banff classi-

fication, it becomes an especially useful tool to accurately determine the diagnosis (Sellarés *et al.,* 2012; Gowrishankar, 2022).

Despite the widespread prevalence of kidney transplants and advances in understanding the pathophysiology of antibody-mediated rejection, there is still no unified approach to the optimal treatment strategy for allograft rejection, particularly for patients with chronic active antibody-mediated rejection (Archdeacon *et al.,* 2011; Velidedeoglu *et al.,* 2018). This is a significant issue in clinical practice considering the poor outcomes of kidney allografts (Mateu *et al*., 2004).

The history of kidney transplantation in Latvia began in 1973 with a transplant from a deceased donor. This practice continues today, utilising both deceased and living donors. Since 2010, on average 56 kidneys are transplanted in Latvia per year. There is data on the frequency and outcomes of kidney transplants in Latvia, but the data on allograft biopsies have not been summarised and analysed.

This study aimed to determine clinical and histopathological characteristics, treatment and short-term outcomes of biopsy-proved kidney graft rejection in Latvia.

MATERIALS AND METHODS

Study population and design. This retrospective observational study reviewed all kidney allograft biopsies performed at the Pauls Stradiņš Clinical University Hospital in Rīga, Latvia, from January 2014 to December 2022. Allograft biopsies for patients aged 18 years or older with a rejection and at least seven glomeruli were included. Kidney transplant rejection was diagnosed according to clinical, laboratory and biopsy-proven acute rejection (BPAR) histological criteria. Further, BPAR was classified and subdivided using Banff classification criteria (Roufosse *et al.,* 2018; Gowrishankar, 2022). Repeated control biopsies after receiving therapy were excluded.

Data collection. Out of the 523 graft biopsies, 153 were further analysed based on meeting the inclusion criteria, which included data on sex, age, number of transplants, and cause of end-stage renal disease. Creatinine levels were evaluated at the time of the biopsy and after a one-year follow-up. Graft function was evaluated according to the estimated Glomerular Filtration Rate (eGFR), calculated with the CKD-EPI Creatinine, 2021 equation (eGFR Calculator, 2024). Treatment strategies for allograft rejection were investigated and treatment outcomes were analysed including changes in kidney function, need for return to kidney replacement therapy or death. An improvement in eGFR of 20% or more from baseline was considered an adequate response to treatment.

Kidney allograft biopsy. The majority of allograft biopsies were performed due to an unexplained increase in serum creatinine or delayed/slow kidney function after kidney transplantation. In our centre, there is no routine for diagnostic biopsies; decisions are primarily based on physicians' experience and judgment. Of all the biopsies, only five were diagnostic biopsies performed at an average of 228 days post-transplant. Both the protocol and the acute biopsies were included in the study and analysed. All biopsies were sent, reviewed, evaluated, and classified at the National Centre of Pathology in Vilnius, Lithuania, according to Banff criteria 2007–2019 (Roufosse *et al.,* 2018; Gowrishankar, 2022). The Banff Lesion Scores assess both the presence and severity of histopathological alterations in various regions of renal transplant biopsies, with a primary focus on, though not limited to, the diagnostic features indicative of rejection. The Banff classification encompasses additional categories, including normal biopsies or other pathologies such as BK-virus nephropathy, calcineurin inhibitor toxicity, and other conditions affecting kidney transplants. This study specifically examined and analysed kidney transplant biopsies in accordance with rejection criteria and classifications, including acute or chronic-active antibody-mediated rejection (AMR), acute cellular rejection (aCR), mixed rejection, and borderline rejection. Histopathological parameters such as glomerulitis (g) and peritubular vasculitis (ptc), which reflect microvascular inflammation and are indicative of antibody interaction with tissue in AMR, as well as glomerular basement membrane double contouring (cg), associated with chronic changes, were reviewed. Additionally, the severity of intimal arteritis (v), a key feature in both AMR and cellular rejection (CR), was evaluated. Tubulitis (t), a defining lesion of CR in kidney transplants that reflects the degree of inflammation within the cortical tubule epithelium, was also considered, along with other histopathological changes, to classify the findings (Roufosse *et al*., 2018).

Immunosuppression. All patients undergoing kidney transplant received either T-cell depleting (anti-thymocyte globulin) or non-depleting (basiliximab) induction immunosuppressive therapy based on their immunological status, such as prior transplant history and sensitisation levels. For maintenance immunosuppression, the majority of the patients (82%, n = 126) received a triple immunosuppressive regimen with glucocorticoids, a calcineurin inhibitor (tacrolimus or cyclosporine) and an anti-proliferative agent (mycophenolate mofetil, mycophenolic sodium or azathioprine). The rest of the patients received different combinations, including mammalian target of rapamycin inhibitors. Medication dosage, drug-level targets and overall immunosuppressive regiment were adjusted according to the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients, 2009, and individual patient clinical status (Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group, 2009).

Rejection treatment. In our centre, allograft rejection treatment is based on available guidelines (Schinstock *et al.,* 2020; Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group2009). For patients with T-cell mediated rejection, treatment includes intravenous steroids and T-cell depleting agents. Pulse glucocorticoids,

plasma exchange and intravenous immunoglobulins with or without rituximab in different combinations is used to treat antibody-mediated rejection. The choice of treatment strategy and dosage of medications depend on individual patient clinical status and characteristics.

Statistical analysis. Data were analysed using descriptive statistics; quantitative data was shown as the mean ± standard deviation (SD). Categorical data were expressed as numbers and percentages. Statistical calculations were performed using Excel 2021. Data was analysed using T-tests. A p value of < 0.05 was considered statistically significant.

RESULTS

Overall, 523 graft biopsies were performed. Of these, 153 met inclusion criteria for the study and were analysed (from total 146 patients) — 29% of graft biopsies were with rejection. Baseline characteristics can be found in Table 1. In 82% (n = 126) biopsies there were 10 or more glomeruli and in 18% (n = 27) there were seven or more, but less than 10 glomeruli. The mean age at transplantation was 45.5 ± 13.98 years. Chronic glomerulonephritis was the most common cause of end-stage renal disease. 12% (n = 19) transplantations were from living donors. Mean time from the transplant to the biopsy was 1175 days. In 56 cases rejection was diagnosed 90 days or less after kidney transplantation, and kidney transplant biopsy was mostly performed because of slow or delayed kidney function after transplantation. There were two or more transplantations in 20 of these cases.

Rejection type and incidence between graft biopsies are displayed in Figure 1. Acute antibody-mediated rejection (aAMR) was diagnosed most often — in 41% cases, followed by chronic-active antibody-mediated (caAMR) — 25%; then mixed rejection (MR) — 16%, acute cellular rejection (aCR) — 10% and borderline rejection — 8%.

Table 1. Baseline characteristics

Male gender, n (%)	84 (57.5%)
Mean age at transplantation, years	45.5 ± 13.98
Cause of end-stage renal disease	
Glomerulonephritis, n (%)	47 (32.2%)
Diabetes mellitus, n (%)	11 (7.5%)
Polycystic kidney disease, n (%)	18 (12.3%)
Arterial hypertension, n (%)	11 (7.5%)
HIN, n (%)	39 (26.7%)
Other, n (%)	20 (13.7%)
Number of transplantations	
One transplantation, n (%)	102 (66.7%)
Two transplantations, n (%)	44 (28.8%)
Three transplantations, n (%)	6 (3.9%)
Four transplantations, n (%)	1 (0.7%)
Living donor transplant, n (%)	18 (11.8%)
Mean interval between transplantation and biopsy, days	1175 ± 1667

HIN, chronic interstitial nephritis

Besides augmented maintenance immunosuppression for almost all patients, pulse glucocorticosteroids (GCS) were the most commonly administered treatment (70% cases), followed by plasma exchange (PEX) in 59%, rituximab (RTX) in 50%, immunoglobulins (IG) in 24% and anti-thymocyte globulin (ATG) in 10% cases, in different, mostly non-homogenous combinations (Fig. 2). Non-adherence and advanced fibrotic changes observed in biopsy, and the presence of significant comorbidities, were the primary factors contributing to the decision not to administer specific treatment, aside from intensified maintenance immunosuppression, which was observed in 16% (n = 25) of the cases.

As mentioned before, treatment interventions were very heterogeneous — overall, 19 different combinations. The most common treatment combinations were with PEX+RTX+GCS (n = 22) and PEX+RTX+GCS+IG (n = 19). There were no statistically significant associations in these treatment combination outcomes in the aAMR group ($p = 0.38$). In addition to PEX+RTX+GCS+IG, one patient received eculizumab.

After one year of treatment, the most favourable outcomes were in the aCR group where mean allograft eGFR increased by +20.7 ml/min, compared to the worst outcome caAMR group where eGFR decreased by – 4.7 ml/min ($p = 0.03$). In the aAMR group, mean eGFR increased by +13.3 ml/min and in MR mean eGFR increased by +12.9 ml/min after one-year treatment. Mean eGFR changes between aAMR and MR compared to caAMR group were statistically significant ($p = 0$ and $p = 0$). (Fig. 3). There were no statistically significant changes in mean eGFR between aCR and aAMR ($p = 0.52$), aCR and MR ($p = 0.51$), and aAMR and MR groups ($p = 0.95$).

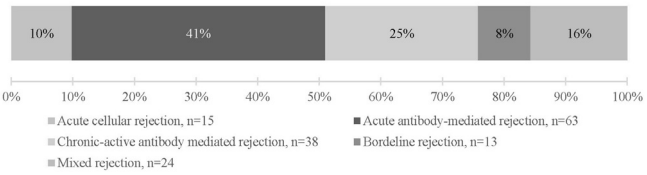

Fig. 1. Rejection type and incidence between graft biopsies.

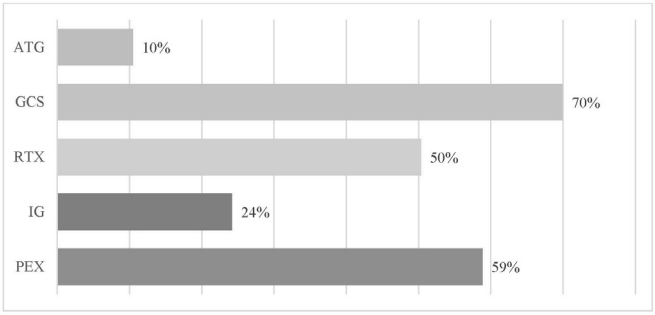

Fig. 2. Administered treatment for allograft rejection according to individual agents or therapy used.

ATG, anti-thymocyte globulin, n = 16; GCS, glucocorticosteroids, n = 107; IG, intravenous immunoglobulins, n = 37; PEX, plasma exchange, n=90; RTX, rituximab, n = 77

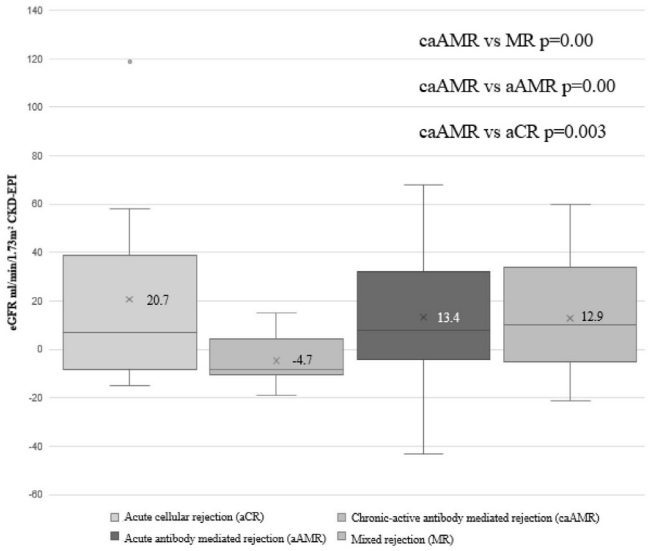

Fig. 3. eGFR changes between grafts after one year of treatment.

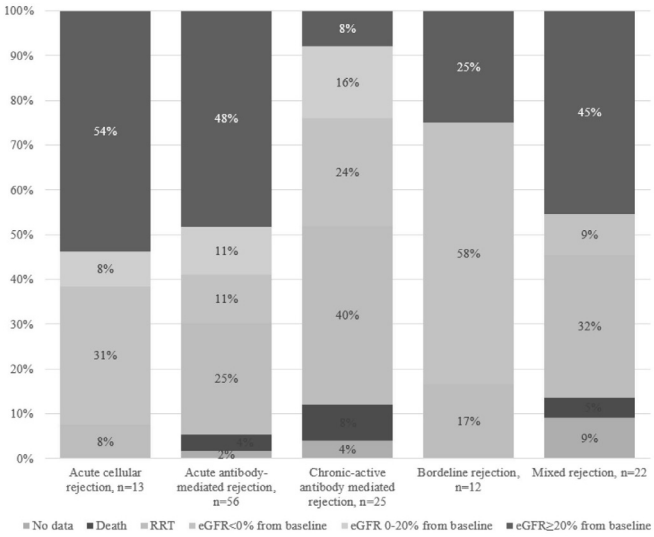

Fig. 4. Treatment outcomes in patients with different Banff diagnostic categories of allograft after one-year treatment.

Evaluating kidney transplant outcomes after one year of treatment in the aCR group, graft function stayed the same or improved in 62% cases, moreover graft function increased ≥ 20% from baseline in 54% cases. Similarly, in the mixed and aAMR group, eGFR increase of ≥ 20% was observed for 45% and 48% cases, respectively, compared to only 6% of patients in the caAMR group. Furthermore, the caAMR group was with the most patients (48%) who returned to dialysis or died (Fig. 4). Overall, 3.9% of patients died.

DISCUSSION

This is the first study that has collected data on clinical and histopathological characteristics, treatment and short-term outcomes of biopsy-proven kidney graft rejection in Latvia. Overall prevalence of BPAR was high (29%) in the study. Different risk factors have been identified — non-immunological and immunological — which can contribute to graft rejection: non-adherence, younger age at transplantation, older donor age, deceased donor, female donor, human leukocyte antigen (HLA) mismatches, and physician-derived under-immunosuppression (Foroutan *et al.,* 2019; Oweira *et al.,* 2022). In the study, the majority (84%) of the kidneys were from deceased donors and mean recipient age was 45.5 years. Living donors have better outcomes than deceased donors because of reduced cold and warm ischaemia time, better preparation and evaluation before transplantation and immunological compatibility (Oweira *et al.,* 2022; Chkhotua *et al.*, 2003). The study showed that living donation is not very prevalent in Latvia. Living donation can be a daunting and challenging prospect, and therefore it is essential to provide proper education about surgery, including its short-term and long-term risks, in a timely manner to both recipient and their potential donors. Non-adherence to immunosuppressive therapy can have several severe consequences, including allograft rejection, loss and patient mortality (Loghman-Adham, 2003; Hucke *et al.,* 2017). Our data showed that the worst short-term outcomes after one-year treatment were in the caAMR group, where not only mean eGFR changes were the lowest among groups, but almost half of the patients returned to dialysis or died after one year. This reflects the allograft rejection`s clinical importance, which is a significant issue worldwide (Sellarés *et al.,* 2012). In a multicentre cross-sectional cohort study carried out in the USA and Canada with 173 patients, antibody-mediated injury caused allograft dysfunction late post-transplant in 57% of renal transplant recipients (Robert *et al.,* 2010). AMR starts with donor-specific alloantibody (DSA) formation against HLA, ABO, and rarely non-HLA antigens which further interacts with microvascular endothelial cells leading to allograft dysfunction by different mechanisms (Farkash *et al.,* 2012). Unlike aAMR, caAMR is a long-term, slowly progressive and often clinically silent immunological process, which takes months to years (Hara, 2017), so it was not surprising that in our study, mean time from kidney transplantation to caAMR was 2661 ± 1908 days. Various strategies have been used to manage antibody-mediated rejection, with mixed combinations of variable intensity plasmapheresis, different dosage and timing of immune globulins with or without B-cell depleting agents, variable use of glucocorticoids, and complement system inhibitors. These approaches are mostly based on small studies with heterogeneous patient populations, which naturally creates challenges in the interpretation of treatment effects. Given the extent of the severe problem, it is pitiful that optimal treatment schemes or commonly accepted guidelines are still not approved (Velidedeoglu *et al.,* 2018; Schinstock *et al.,* 2020).

In our study, in 56 cases, rejection was detected in the first three months after receiving an allograft and in 20 of them it was retransplantation. It is known that DSA can pre-exist before or develop after kidney transplantation (de novo DSA). Pre-existing DSA can form after blood transfusion, pregnancy or prior transplantation (Schinstock *et al.,* 2020).

As previously mentioned, DSA has a significant role in the pathogenesis in allograft rejection. Pre-existing DSA, HLA mismatch could lead to an increase in the rate of acute rejections, as observed in our study (Oweira *et al.,* 2022; Santos *et al.,* 2017). Unfortunately, in our centre, DSA testing was not available for quite a long time, which might have improved outcomes.

In our centre, graft rejection treatment, similarly as in other centres, is based on overall available evidence and guidelines (Schinstock *et al.,* 2020). Therapy varies in the types and combinations of drugs used among patients, making highly heterogeneous groups with small numbers of patients, making it hard to draw definitive conclusions. The most commonly used treatment combinations were with PEX+RTX+GCS with or without IG, but there were no statistically significant associations in the aAMR group. In our centre, a therapeutic approach is highly individual, influenced by the findings on allograft biopsy, patient clinical status, medication availability and associated costs and, of course, experience of the physician. That could explain the wide heterogeneity of the treatment regiments. In this study, the highest incidence of death was in patients with caAMR. The cause of death was not analysed, but considering the wide range of treatment options for allograft rejection and the depth of immunosuppression after the treatment, the treatment can be a risk factor for infection development (Gupta *et al.,* 2024). In a prospective study in Switzerland, infectious complications and graft outcomes were analysed after aAMR treatment. In the study, almost 64% recipients developed an episode of infection, mostly (43%) bacterial and after one year two patients had died due to severe infection (Perrottet *et al.,* 2021).

Overall, this is the first study to compile Latvian data on biopsy-proven allograft rejection, detailing its clinically histological characteristics along with short-term outcomes. It provides valuable insight into the issues within Latvia. Future studies in this area are essential, as they would significantly enhance daily clinical practice, inform decisions about immunosuppressive therapy protocols and improve selection of patients who genuinely need therapy, considering risks and poor outcomes, especially with chronic changes. The limitation to our study is that it is a retrospective analysis with a relatively small patient sample, which restricted our ability to include various other parameters due to incomplete data for some patients. Immunological evaluation, such as assessing panel-reactive antibodies, HLA mismatch, and DSA, which directly affect kidney transplant outcomes, were not conducted in this study. Although trends in kidney transplant function after one year of treatment are evident, it is crucial to assess broader clinical outcomes post-treatment, including reasons for graft loss. This information is particularly important for making treatment decisions, especially if outcomes are associated with treatment risks, such as infections (Gupta *et al.,* 2024).

In conclusion, overall biopsy-proven acute rejection prevalence between kidney graft biopsies was high. Antibody-mediated rejection was diagnosed most often with the least favourable short-term outcomes. Despite various improvements in immunosuppression, caAMR remains a serious cause of transplant dysfunction or loss.

ETHICS

The study is in accordance with the 1964 Declaration of Helsinki and its later amendments. This study is approved by the Ethics Committee of Pauls Stradiņš Clinical University Hospital, protocol number 200524-6.

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BIOPSIJĀ APSTIPRINĀTU NIERES TRANSPLANTĀTU TREMES KLĪNISKI HISTOPATOLOĢISKAIS RAKSTUROJUMS LATVIJĀ

Daudziem pacientiem ar terminālu nieru mazspēju nieres transplantācija ir vēlamākā nieru aizstājterapijas metode, tādējādi uzlabojot dzīves kvalitāti. Pēdējos gados nieres transplantācijas iznākumi ir uzlabojušies, tomēr transplantāta atgrūšana joprojām ir nopietna problēma klīniskajā praksē. Šī retrospektīvā pētījuma ietvaros tika izskatītas nieres transplantātu biopsijas, kas veiktas Paula Stradiņa Klīniskajā universitātes slimnīcā no 2014. gada janvāra līdz 2022. gada decembrim. Pētījuma mērķis ir izpētīt nieres transplantāta biopsijā apstiprinātu atgrūšanas klīnisko un histopatoloģisko raksturojumu, pielietotās ārstēšanas metodes un īstermiņa iznākumus Latvijā. Transplantāta atgrūšana tika diagnosticēta, ņemot vērā histoloģiskos, klīniskos un laboratoriskos kritērijus; turpmāk klasificēta, pamatojoties uz *Banff* klasifikāciju (kopā piecas grupas). Tika analizētas ārstēšanas metodes, laboratoriskie dati biopsijas laikā un pēc gada. Tika iekļautas 153 transplantātu biopsijas. Lielākā daļa nieres transplantātu bija no miruša donora. Neskaitot pastiprinātu bāzes imūnsupresīvo terapiju gandrīz visiem pacientiem, glikokortikosteroīdu pulsa deva bija visbiežāk pielietotā ārstēšana, kurai sekoja plazmas apmaiņa, rituksimab, imūnglobulīni un anti-timocītu globulīns dažādās, ne-homogēnās kombinācijās. Visbiežāk diagnosticēja akūtu antivielu mediētu tremi. Vislabvēlīgākie iznākumi pēc gada, ņemot vērā, nieres transplantāta funkciju, bija akūtas celulāras tremes gadījumā salīdzinot ar nelabvēlīgāko hroniskas-aktīvas antivielu mediētas tremes grupu (ha-AMT) (p = 0.03), turklāt ha-AMT grupā pēc gada bija visvairāk pacientu, kuri atgriezās dialīzē vai nomira.