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Research Article

Evaluating The Clinical Relevance Of Antibodies Againstnon-Human Leukocyte Antigen In Kidney Transplantation.

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Abstract

For eligible patients with end-stage kidney disease (ESKD), kidney transplantation is the recommended form of kidney replacement therapy since it has been shown to lower death rates, enhance quality of life, and be more affordable than dialysis. Although the risk of rejection has decreased due to recent developments in donor-specific antibody (DSA) detection and human leukocyte antigen (HLA) typing, antibody-mediated rejection (AMR) can still happen in the absence of DSA. According to earlier research, antibodies against non-human leukocyte antigens (non-HLAs) may be the cause of rejection.

Our goals were to learn more about the distribution and prevalence of non-HLA antibodies in our community, try to link these results to graft outcomes, and discover whether non-HLA antibodies might be used to identify graft dysfunction and impairment. Methods: From January 2010 to December 2020, we performed a retrospective analysis on kidney transplant recipients. All of the participants were over the age of 18, had received kidney transplants alone, were compatible with both ABO and HLA, and were matched at the A, B, and DR loci (mismatch 0:0:0). At the time of transplantation, HLA testing came out negative.

Using the One Lambda LABScreenTM, Autoantibody kit groups 1, 2, and 3, as well as the Immucor LIFECODES non-HLA autoantibody assay, the samples from the control group and the early graft rejection cases were examined for non-HLA antibodies. Findings: Out of the 850 kidney transplant recipients, 12 developed early graft rejection within the first month following their procedure, and 18 did not. These patients were chosen as study controls. Due to a small sample size, our study found no association between early rejection and the overall burden of non-HLA antibodies. However, a sub-analysis showed that rejection was linked to certain high-frequency pre-transplant non-HLA antibodies identified by LIFECODES, including GSTT, CXCL11, CXCL10, and HNR (Fisher's exact test with Bonferroni correction, $p < 0.001$).

Following transplantation, the majority of pre-transplant non-HLA antibody levels decreased, which was explained by immunosuppression. Conclusion: Although the overall relationships between the burden of non-HLA antibodies and rejection episodes are still unclear, the "high frequency" non-HLA antibodies showed a correlation with graft rejection. The rebound phenomena of non-HLA antibodies, the long-term generation of de novo non-HLA antibodies, and their effects on graft survival require more research.

Keywords : *Snon-human leukocyte antibodies; graft rejection; kidney transplantation.*

INTRODUCTION

When compared to dialysis patients, kidney transplantation is the gold standard for kidney replacement therapy for individuals with end-stage renal disease (ESKD) and is linked to better mortality and morbidity outcomes [1]. Donor-Specific Antibodies (DSAs) against the Human Leucocyte Antigens (HLAs) in the transplanted kidney may have an impact on the clinical results after kidney transplantation. These antibodies have the potential to reduce kidney allograft survival and induce antibody-mediated rejection (AMR) in the transplanted kidney [2]. Nevertheless, humoral rejection may still happen in certain individuals without DSA, and a number of studies have linked the existence of antibodies against non-Human Leucocyte Antigens (non-HLAs) to graft rejection [3,4]. to the existence of antibodies directed against non-HLAs, or non-human leukocyte antigens [3,4]. The incidence and clinical significance of non-HLA antibodies in kidney transplantation are still poorly known, despite the fact that the function and significance of HLA-specific antibodies in kidney transplantation and subsequent graft loss have been thoroughly investigated [5,6]. Non-HLA antibodies

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have occasionally drawn attention over the years due to their prevalence and potential clinical implications for kidney transplant recipients' health outcomes. It is mostly unknown what causes the production of non-HLA antibodies. Antigenic determinants of targets for nonHLA antibodies are shielded from immune monitoring under normal physiological settings, but they become accessible following trauma or tissue damage.

This damage may happen during dialysis prior to transplantation, during retrieval, or during the implantation or rejection of allografts. At that moment, the presentation and release of non-HLA antigens may trigger an immunological reaction. Vascular receptors, adhesion molecules, intermediate filaments, and minor histocompatibility antigens are just a few of the antigens that non-HLA antibodies might target. For instance, antibodies against Vimentin antigens, Polymorphic MHC class I-related chain A (MICA), Endothelial-1 Type A receptors (ETARs), and Angiotensin II Type 1 receptor (AT1R) have been found [7–10].

Non-HLA antibodies that recipients of kidney transplants may have could trigger an immune response against cells in the transplanted kidney's microcirculation, starting an inflammatory process that could lead to antibody-mediated allograft rejection [11,12].Because of the genetic distribution within the local population and environmental conditions, the targets for these non-HLA antibodies are frequently cryptic and may also vary by location [13].

Non-HLA antibodies cause a memory response and alter the patient's active immune status, resulting in an overlap between autoimmunity and alloimmunity [14]. The purpose of this study was to better understand the distribution and prevalence of non-HLA antibodies in our community and make an effort to Analyze whether non-HLA antibodies can be used as a clinical marker to identify graft dysfunction or impairment and link these results with graft outcomes.

MATERIALS AND METHODS

Study Design and Study Population

When compared to dialysis patients, kidney transplantation is the gold standard for kidney replacement therapy for individuals with end-stage renal disease (ESKD) and is linked to better mortality and morbidity outcomes [1]. Donor-Specific Antibodies (DSAs) against the Human Leucocyte Antigens (HLAs) in the transplanted kidney may have an impact on the clinical results after kidney transplantation.These antibodies have the potential to reduce kidney allograft survival and induce antibody-mediated rejection (AMR) in the transplanted kidney [2]. Nevertheless, humoral rejection may still happen in certain individuals without DSA, and a number of studies have linked the existence of antibodies against non-Human Leucocyte Antigens (non-HLAs) to graft rejection [3,4].

The One Lambda, LBScreenTM Autoantibody kit groups 1, 2, and 3 (LABScreen) [15,16] and the Immucor LIFECODES non-HLA autoantibody test (LIFECODES) [17,18] were used to check the samples for non-HLA antibodies. Both kits cover a large variety of non-HLA antibody targets and make use of Luminex bead technology. 60 non-HLA antigen targets are covered by the LIFECODES kit, compared to 39 by the LABScreen kit. We prospectively gathered and stored each patient's demographic information in our hospital's electronic database, including age, gender, ethnicity, primary diagnosis, kidney replacement therapy (KRT) modality, dialysis vintage, transplant type, rejection type (antibody, cellular, and mixed), and rejection severity.

Detection of Non-HLA Antibodies

The LIFECODES and LABScreen autoantibody assays were used to retrospectively check the serum samples taken before and after transplantation for the presence of non-HLA antibodies. The vendor determines the cut-off MFI for each non-HLA target. When the estimated MFI exceeded the predetermined cut-off (or when MFI is greater than 95%), antibodies were classified as positive for a particular target.

One Lambda, LABScreenTM Autoantibody Kit Groups 1, 2, and 3 Testing Technique

The LABScan™ 3D S066 apparatus (LABScan 3D) from Thermo Fisher Scientific, Waltham, MA, United States, was used to gather raw data for the LABScreen autoantibody assay testing. After 10 minutes of microfuging the sera at 13,000 rpm, 20 µL of test, negative, and positive control serums were added to the 5 µL autoantibody bead mix in a 96-well plate. The plate was placed in the dark at room temperature for half an hour after being sealed with a tray seal. After washing the plate with 150 µL of wash buffer, it was centrifuged for five minutes at 1800 × g.

After flicking the wash buffer out of the wells, 200 µL of wash buffer was used twice more to wash the plate. Each well received 100 µL of 1×PE-conjugated goat antihuman IgG (50 ng/µL), which was then combined using a pipette. After sealing the tray, it was let to sit at room temperature in the dark for half an hour. After that, 200 µL of wash buffer was used to wash the plate three times as before. Using a multichannel pipette, 80 microliters of PBS were added to each well and combined. After that, the beads were moved to a low-profile plate and subsequently to the LabScanTM 3D. FLEXMAP 3D® software version 4.2 was used to acquire the data, and HLA Fusion Research software version 6.4 was used to analyze the results of the LabScreen.

Immucor LIFECODES Non-HLA Autoantibody Assay Testing Technique

In order to test the Immucor LIFECODES non-HLA autoantibody

assay, 40 µL of LIFECODES beads in a 96-well plate were combined with 10 µL of positive control, negative control, and test serum using a pipette after the sera had been microfuged for 10 minutes at 13,000 rpm. Following that, the plate was sealed with a tray and allowed to sit at room temperature for 30 minutes in the dark. After that, the plate was centrifuged at 1300× g for five minutes after being cleaned with 150 µL of wash buffer. After flicking the wash buffer out of the wells, 200 µL of wash buffer was used twice more to wash the plate. In wash buffer, the conjugate that included with the kit was diluted 1:10. Each well received fifty microliters of conjugate, which was then combined. After sealing the tray, the plate was let to sit at room temperature in the dark for half an hour. After that, 200 µL of wash buffer was used twice to wash this plate.

The wells were filled with 150 microliters of wash buffer. After being mixed with a pipette to resuspend the beads, they were moved to a low-profile 96-well plate. The LABScanTM 3D with FLEXMAP 3D® software was used to acquire the data, and the LIFECODES non-HLA antibody analysis tool was used to examine the findings.

Kidney Allograft Biopsies, Histological Grading, and Treatment of Graft Rejection

All kidney transplant recipients who had an allograft biopsy recommendation during the post-transplant follow-up within a month of receiving a kidney transplant were included in this group. When graft malfunction (i.e., eGFR drop, proteinuria, or delayed graft function) occurred, the biopsies were conducted. According to the most recent Banff 2019 consensus, an accredited pathologist evaluated and scored each biopsy for T-cell-mediated rejection (TCMR) and antibody-mediated rejection (AMR) [19].

STATISTICAL ANALYSIS

For categorical variables, descriptive statistics are presented as numbers and percentages, and p-values were ascertained using the Chi-square test. The Mann-Whitney U test was utilized to ascertain p-values, and the continuous variables are represented as the median and interquartile range. The associations between various patient characteristics and the existence of non-HLA antibodies before and after transplantation were estimated using univariate and multivariable logistic regression analysis. A p-value was deemed statistically significant if it was less than 0.05. To ascertain whether two category variables had non-random relationships, the Fisher's exact test was employed. In order to determine the adjusted p-value for multiple tests, the Bonferroni correction was also applied. IBM SPSS version 26, which is registered with the University of Manchester, was used to analyze the data.

RESULTS

Demographic Data of the Study Population

Thirty patients were chosen for additional analysis for this study out of the 850 kidney transplant recipients who had screening. According to the study's inclusion criteria, 18 patients served as controls, and 12 patients experienced early graft rejection, or rejection that happened less than a month after transplantation. Seven patients (23%) received a kidney transplant from a living donor, while 23 patients (77%) received a kidney allograft from a deceased donor. The cohort's mean age was 52 years, and the majority of its members were white (77%), with 70% of them being men. The cohort's median dialysis vintage was 26 months. Overall, there were no statistically significant variations between the two groups' baseline characteristics.

Pre and Post-Transplant Non-HLA Antibodies in Early Graft Rejection and Control Groups Using LABScreen Autoantibody

Assay Testing Kit

Using the LABScreen One Lambda Kit from Canoga Park, CA, USA, the distribution of non-HLA antibodies in the control and graft rejection groups before to and following kidney transplantation is displayed. Pre-transplant non-HLA antibodies (HR = 1.03; 95%CI 0.89–1.17; p = 0.69) and post-transplant non-HLA antibodies (HR = 0.89; 95%CI 0.73–1.08; p = 0.25) measured by the LABScreen autoantibody assay testing kit did not statistically significantly correlate with biopsy-proven rejection, according to logistic regression analysis.

Trajectory in Non-HLA Antibody Levels in Pre- and Post-Transplant States

factors, such as prescribing Basiliximab as an induction agent on days 0 and 4 after the transplant procedure, followed by maintenance treatment with Tacrolimus, Mycophenolic acid, and +/- Prednisolone depending on the patient's body weight and immunological risk. Following kidney transplantation, autoantibody assay testing using the LABScreen and LIFECODES testing kits revealed a decrease in the overall antibody load for the control and early graft rejection groups.

Other Predictors of Graft Rejection

Our study investigated the relevance of non-HLA antibodies in this context as well as additional possible predictors for graft rejection. Notably, early graft rejection (cellular, humoral, or mixed) within the first month following kidney transplantation was unrelated to age, gender, ethnicity, or type of KRT.

DISCUSSION

Between January 2010 and December 2020, our center successfully completed 850 unsensitized single kidney transplant patients that were entirely matched at the A:B:DR loci (0:0:0) and had an estimated reaction frequency of 0%. Using two separate autoantibody assay testing kits, LIFECODES and LBScreen, we assessed the non-HLA antibody response of study controls and early graft rejection cases to a variety of non-HLA antigens both before and after kidney transplantation. Our study found no significant correlation between the overall burden of non-HLA antibodies and early graft rejection, which was likely due to the small study sample size [3,4]. However, the presence of non-HLA antibodies may have raised the risk of donor DSA and subsequent graft rejection. early graft rejection, which was most likely brought on by the study's small sample size [3,4]. However, according to a sub-analysis, graft rejection was linked to particular "high frequency" pre-transplant non-HLA antibodies, such as GSTT1, CXCL11, CXCL10, and hnRNPK, which were identified by LIFECODES testing. There isn't a single histopathological characteristic or phenotype that is unique to non-HLA antibodies and their expression patterns, either by itself or in conjunction with HLA-DSA, due to the diversity of non-HLA antibody targets and tissue expression patterns [20].

Although not many non-HLA antibodies have been thoroughly investigated in the medical literature, solid organ transplantation (SOT) and hemopoietic stem cell transplantation (HSCT) have shown their effects on graft survival and patient morbidity. 419 liver transplant recipients participated in a study published by Aguillera et al. [21].

(HSCT). 419 liver transplant recipients participated in a study published by Aguillera et al. [21]. De novo immune-mediated hepatitis and transplant failure occurred in 70% of patients whose Glutathione S-transferase theta 1 (GSTT1) genotype did not match that of their donor. Similar negative effects of GSTT1Abs, either by themselves or in conjunction with HLA-DSAs, on kidney graft success were noted by Comoli et al. [22]. In their investigation of GSTT1's function in cardiothoracic transplantation, Yeo et al. [23] showed that pre-transplant anti-GSTT1 antibodies that appeared after transfusion are linked to a higher risk of acute allograft rejection. The synthesis of anti-GSTT1 antibodies and their role in hepatic Graft-versus-Host Disease (GvHD) following HSCT were examined by Martinez-Bravo et al. [24]. Additionally, a higher risk of acute and chronic GvHD is linked to GSTT1 donor/recipient mismatches.

Additionally, research was done on the function of anti-heterogeneous nuclear ribonucleoprotein-K (hnRNPK) antibodies in solid organ transplants. The role of anti-hnRNPK antibodies, a subtype of non-HLA antibody, in the emergence of cardiac allograft vasculopathy (CAV) in heart transplant recipients was investigated in a study by Acevedo et al. [25]. Intravascular ultrasonography (IVUS) and angiography are used to diagnose CAV. In order to find antibodies, this study examined serum samples from 48 heart transplant recipients. As a novel antigenic target for the development of CAV, the researchers discovered hnRNPK. When compared to patients without CAV, those with CAV identified by IVUS or angiography had noticeably greater levels of antihnRNPK antibodies.

Regardless of the diagnostic method used, this study indicates that anti-hnRNPK antibodies are statistically linked to CAV illness after heart transplantation.

One would anticipate a large rise in immune cells infiltrating the allograft during kidney transplantation. The release of chemokines from parenchymal cells and the increase of endothelial adhesion molecules aid in this process. 44 patients with acute allograft rejection exhibited greater serum levels of chemokines (such as CXCL1, CXCL5, CXCL6, CCL2, CCL21, and especially CXCL10) and CX3CL1 prior to transplantation, according to Krupicekova et al. [26], which suggested a stronger inflammatory state.

In the end, our sample population is too small to make any meaningful connections between histopathological alterations in graft rejection and the existence of non-HLA antibodies. More research is required to ascertain the precise importance and pathogenic potential of these findings, as well as whether there are any practice-changing consequences, even though our data do highlight the possible relevance of serum reactivity to a single non-HLA autoantigen. The majority of pre-transplant non-HLA antibody levels decreased after transplantation, according to the cross-sectional investigation, which was conducted using a typical induction and maintenance immunosuppression approach for kidney transplant recipients at our center.

Themethodofinductionandmaintenanceimmunosuppression used here may have been the cause of this. In order to better understand the rebound phenomena of non-HLA antibodies, the emergence of de novo non-HLA antibodies after kidney transplantation, and their effects on graft survival, more longitudinal data is needed. We were unable to give direct proof of the role of non-HLA antibodies in graft rejection since we lacked the necessary staining kits for our graft rejection biopsy samples. For this investigation, we tested for non-HLA antibodies using testing kits from two vendors. However, it was challenging to get precise interpretations of the influence of this metric from our limited cohort sample size.

Among other things, the disparity in detection sensitivity, range, or epitope coverage may be the cause of the two kit test protocols' lack of agreement. It seems that the LIFECODES testing kit is more sensitive in detecting antibodies linked to rejection. Longer-term fundamental and translational research will be required in the future to identify the relationships between non-HLA antibodies and

acute tissue damage as well as to differentiate between the effects of de novo and persistent non-HLA antibodies on transplant survival. It would be desirable to implement follow-up confirmation assays using other orthogonal quantitative techniques to validate the "high frequency" non-HLA antibodies.

CONCLUSION

In conclusion, compared to HLA antibodies, non-HLA antibodies are less common and less polymorphic. Although the overall relationships between the burden of non-HLA antibodies and rejection episodes are still unclear, our investigation found a large number of "high frequency" non-HLA antibodies that showed a correlation with graft rejection. Larger sample numbers and prospective multi-center investigations are required to further elucidate the function and significance of non-HLA antibodies in kidney transplantation.

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