Case Report

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Quick Response Code:

Website: www.ajts.org

DOI: 10.4103/ajts.AJTS_1_18

Role of *de novo* DQ donor-specific antibody in antibody-mediated rejection in renal transplant recipient: A case study

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Abstract:

The human leukocyte antigen (HLA) matching plays an important role in determining the clinical outcome of renal transplantation. The development of donor specific antibodies (DSA) against HLA is associated with antibody mediated allograft tissue injury, poor outcome and rejection. The DQ-DSA develops in a denovo pattern and its unfavorable impact on renal transplantation has not yet been widely reported. We investigated the clinical significance of DQ-DSA in a patient diagnosed with hypertension, CKD stage V on maintenance hemodialysis (MHD) for second renal transplant. The histocompatibility workup before the first transplant included low resolution HLA-A, B, DR typing of both patient and donor. HLA type of the patient was HLA-A*29, 68, HLAB*44, 44, DRB1*07, 11. HLA type of the donor was HLA-A*03, 68, HLA-B*39, 44, DRB1*07, 10 with a 3/6 match. The HLA antibody screen and complement dependent cytotoxicity crossmatch (CDC) were found to be negative. No therapeutic plasma exchanges (TPE) were done during stay and post-transplant the patient was on triple immunosuppressant therapy. After four years the patient was diagnosed with recurrent membranoproliferative glomerulonephritis and second renal transplant was planned, therefore, histocompatibility workup was initiated. HLA antibody screen was found to be positive for HLA class II. Initially only HLA-A, B, DR typing was performed and that too only low resolution, further, high resolution HLA typing was done for HLA-DR and DQ to rule out if these antibodies are de-novo DQ/DR DSA. We analyzed that the patient had developed de-novo DSA against HLA-DRB1*10:01 (DR10), MFI-2374 and DQB1*06:01 (DQ6), MFI-15315. This study suggests the role of DQ antibodies in determining the graft survival and to highlight the need of HLA DQ typing as a routine of the diagnostic work-up in a solid organ transplant.

Keywords:

Complement-dependent cytotoxicity crossmatch, *de novo* donor-specific antibodies, donor-specific antibodies, human leukocyte antigen

Introduction

The importance of human leukocyte antigen (HLA) matching on the outcome of renal transplantation has been recognized. The exposure to "nonself" HLA molecules after blood transfusion, pregnancy, or organ transplantation in patients may result in the development of anti-HLA antibodies.[1-3] The antibodies which develop posttransplantation against foreign graft HLA are considered as *de novo* anti-HLA donor-specific antibodies (*de novo* DSAs).[3] The *de novo* DSAs are associated with antibody-mediated injury and allograft failure, with a higher impact of HLA Class II DSA than Class I.[4-7] Most of the studies have evaluated the role of DR antibodies, and only a few reports have elaborated the role of DQ antibodies.[8] Both

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Submission: 06-01-2018
Accepted: 15-05-2018
Published: 03-12-2019

How to cite this article: Chowdhry M, Patel M, Thakur Y, Sharma V. Role of *de novo* DQ donor-specific antibody in antibody-mediated rejection in renal transplant recipient: A case study. Asian J Transfus Sci 2019;13:136-9.

α and β chains in DQ molecules express polymorphism unlike HLA-DR antigens, and therefore, *de novo* DSA antibodies could be formed against both α and β chains.[9] This could be responsible for this higher prevalence and strength of the DQ antibody category. This study was done to emphasize the role of DQ antibodies on the graft survival and to stress the need of HLA DQ typing as a part of the diagnostic workup in a solid organ transplant.

Case Report

A 47-year-old male patient diagnosed with hypertension (since 1999), who was nondiabetic, and diagnosed with chronic kidney disease Stage V (~2012) on maintenance hemodialysis (MHD) (10/months) since February 2016 was admitted in our hospital for a second renal transplant. His blood group was O positive. The first renal transplant was done in June 2012. The donor was his 62-year-old mother of the same blood group. His histocompatibility workup before the first transplant included low-resolution HLA-A, B and DR typing of both patient and donor. HLA type of the patient was HLA-A*29, 68; HLAB*44, 44; and DRB1*07, 11. HLA type of the donor was HLA-A*03, 68; HLA-B*39, 44; and DRB1*07, 10 with a 3/6 match. His HLA antibody screen and complement-dependent cytotoxicity crossmatch was negative. No therapeutic plasma exchanges were done during stay and posttransplant, and he was on triple immunosuppressant (solumedrol + mycophenolate + tacrolimus). The patient was discharged and had no complaints until March 2014. A causal biopsy was done, and chronic active antibody-mediated rejection (AMR) with C4d positivity, thrombotic microangiopathy, and immunofluorescence IgA positivity suggestive of recurrent membranoproliferative glomerulonephritis was diagnosed. His serum creatinine level gradually increased to 5 mg/dl since then. He was managed on MHD and second renal transplant was planned, and histocompatibility workup was started. HLA antibody screen was done and found to be positive for HLA Class II. Panel reactive antibody showed HLA Class I 0% and II value 97%. Single-antigen bead (SAB) assay for HLA Class II showed multiple HLA Class II antibodies with varying mean fluorescent intensities (MFIs) (1017–17761). Since initially, only HLA-A, B, and DR typing was performed and that too only low-resolution and high-resolution HLA typing was done for HLA-DR and DQ to ascertain if these antibodies are *de novo* DQ/DR DSA. On analysis, it was clear that the patient had developed *de novo* DSA against HLA-DRB1*10:01 (DR10), MFI-2374 and DQB1*06:01 (DQ6), and MFI-15315.

Discussion

It is now well known that the *de novo* DSAs are associated with a detrimental effect on the graft function.[10] The impact of DSA against HLA-A, B, and DRB1 is well known. However, the incidence of DQ DSA is either underreported or overlooked.[10-12] It is now well established that DQ antibodies are the most common *de novo* DSA detected posttransplant and have a negative effect on the graft survival and function.[10-12] With the advent of sensitive techniques such as luminex-based assays for antigen and antibody detection, it is now possible to detect antibodies most accurately (including DQ antibodies) and antigens more precisely. Here, we report a case of *de novo* DQ antibodies along with DR antibodies. Most of the studies on Class II antibodies focus on DR antibodies. Various studies have reported a percentage rate of 33%–90% for *de novo* DQ antibodies. This is because different centers have different cutoff limits of MFI, especially for Class II antibodies. The other significant reasons are posttransplant follow-up time, implementation of protocol biopsy, follow-up strategy after transplant, different techniques, and assay used for detection. The time taken for the *de novo* antibody to develop differs from patient to patient but generally is formed 6-month posttransplant. However, there is a delay in detection if antibodies other than DQ are also present. This cohort of DQ + non-DQ antibodies takes around 11 months for detection.[10] In our case, the antibodies were detected around 24-month posttransplant and comprised of both DQ and non-DQ antibodies. This may be because the patient was not on follow-up and presented himself only when the renal function was disturbed including an increase in the serum creatinine and development of proteinuria. Since the development of DSA happens much before the actual renal dysfunction sets in, we postulate that these *de novo* antibodies should have been formed much earlier. Furthermore, the presence of DQ in conjunction with other Class I and Class II antibodies has an inferior cumulative effect on the graft survival. The HLA mismatch is an important factor in the development of *de novo* DSA. Zero-mismatched patients seldom develop *de novo* antibodies.[10] In our case, there were three of six mismatches.

Since DQ typing was not done initially, DQ mismatch could not be ascertained. However, it was evident later that patient–donor had a DQ mismatch which contributed to the development of the antibodies. Through this case study and keeping in mind the importance of DQ typing, we suggest that the DQ locus typing should be introduced as a matching parameter in organ allocation algorithms. Although the well-known strong association between HLA-DR and HLA-DQ specificities may result in a good DQ matching in the presence of a good DR matching due

to linkage disequilibrium, a proportion of patients may still present with DQ mismatch. Tagliamacco *et al*., in their study, observed that one of their two fully matched DR patients developed anti-DQ antibodies, leading to chronic AMR.[11] Several other reports have supported that DQ locus typing should be included as a matching parameter in organ allocation algorithms.[5,10,13-15] The MFI value at which the graft is rejected generally happens to be >4000.[10] The DQ antibodies in the present case had an MFI of around 15,000. It has also been proved that the strength of the MFI is directly proportional to the graft loss and the outcome. It has also been reported that these DQ antibodies are more resistant to antirejection or desensitization protocols, and therefore should be detected early.[10] The more the MFI levels, the greater the chance of developing rejection and resistance to desensitization.

DeVos *et al*., in a prospective study, investigated that donor-specific HLA-DQ antibodies were the most commonly detected antibodies contributing toward inferior graft outcome in posttransplant cases.[10] In their study, the patient serum was prospectively monitored for DSA for 1, 3, 6, 9, and 12-month posttransplant, every 6 months thereafter, and during episodes of graft dysfunction or rejection. They found that the majority of DSA occur within 6 month-posttransplant. The MFI cutoff for the presence of *de novo* DSA was more than 2000 for flow cytometric crossmatch as per their protocol. Similarly, Cooper *et al*. found that most DSAs are detected within 6 month-posttransplant.[16] However, Zhang *et al*. reported that most DSAs are formed within 1-month posttransplant and the rest are formed within 6 month-posttransplant.[17]

In our setting, as a protocol, the determination of DSA posttransplant is not done routinely. The presence of *de novo* DQ and other antibodies can be detected only if posttransplant monitoring through DSA determination in regular interval is employed as a strategy. Since the appearance of dnDSA occurs much before the subclinical injury and clinical dysfunction,[5] it should be worthwhile to adopt the strategy of protocol DSA for 6 month-posttransplant.

The characterization of the DQ antibodies is equally important and requires relative expertise. The HLA-DQ antigen is a α and β heterodimer of the HLA Class II type.[9] Both α and β chains in DQ molecules express polymorphism unlike HLA-DR antigens, and therefore, *de novo* DSA antibodies could be formed against both α and β chains. Although it is apparent that alloimmunization is usually and dominantly directed to the β chain, both chains contribute to the complete structure and can induce an immunologic response.[9] Mostly, the β chains are identified and interpreted, and α chain is neglected. This practice may lead to skipping of some antibodies which are otherwise clinically significant as well as incorrect characterization of the antibodies which are otherwise nonsignificant. Therefore, it is important to understand the complex structure and the correct characterization of these antibodies. In our case, the DQB1 antibodies were involved, but the possibility of an HLA-DQα should also be assessed in each case. Furthermore, the presence of allele-specific antibodies is far more frequent in DQ due to a higher rate of DQ alloimmunization and higher rates of misinterpretation of the DQ antibodies and, therefore, warrants attention. To resolve the ambiguities and correct assignment for DQ antibodies, multiple antibody detection assays and techniques and extended high-resolution DQA1/DQB1 typing for both donor and recipient may be required.[18]

Overall, in this study, we would like to emphasize the role of *de novo* DQ antibodies, whose significance and impact on the graft survival has been underestimated and reported. Furthermore, the need to ascertain these antibodies with sensitive techniques such as SAB and perform HLA-DQ typing in the donor to determine DSA should be a part of the protocol for histocompatibility testing in the renal patients. The DQ antibodies either alone or along with other antibodies have an inferior cumulative effect on the graft survival, especially when expressing high MFI. All necessary measures and interventions should be taken in these cases for desensitization and rescue regimens. Posttransplant monitoring through DSA in regular interval should be employed as a strategy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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