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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

The role of nonadherence in donor-specific antibodies formation and their effects on kidney transplant function

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SUMMARY

Introduction Antibody-mediated rejection is one of the leading causes of graft loss after kidney transplant. Donor-specific antibodies (DSAs) are recognized as biomarkers of transplant rejection. The aim of this study was to describe the association between nonadherence and DSA formation.

Case outline A 21-year-old patient underwent a living-related donor kidney transplant procedure in October 2017. The donor had the same blood type as the patient with one mismatch at the HLA-B and HLA-DR loci. The presence of pre-transplant human leukocyte antigen donor-specific antibodies (HLA-DSA) was not confirmed. The postoperative course was uneventful. Three months post-transplant, low tacrolimus levels and consequent increase of serum creatinine were evident. Five months post-transplant, the occurrence of HLA-DSA was confirmed along with *de novo* donor-specific anti-HLA-DQB1*06:04, mean fluorescence intensity (MFI) was 20,725. Acute antibody-mediated rejection of kidney transplant was diagnosed, and the following treatment was applied: corticosteroid pulses, immunoglobulins, and plasmapheresis. Stable graft function persisted over the following one-year period, but over time, low tacrolimus levels, increase in serum creatinine, and proteinuria reappeared. Heteroanamnestic data indicated irregular taking of immunosuppressive drugs and an inadequate hygiene-dietary regimen. Repeated anti-HLA-DQB1*06:04 testing revealed MFI of 5933. Graft biopsy demonstrated elements of chronic active antibody-mediated rejection, acute T-cell-mediated rejection, interstitial fibrosis, and tubular atrophy. Despite repeated anti-rejection therapy, total graft loss occurred.

Conclusion Nonadherence to recommended immunosuppressive regimen brought about the *de novo* HLA-DSA formation as well as production of antibody-mediated and T-cell-mediated rejection, and consequent total loss of kidney transplant function.

Keywords: kidney transplant; nonadherence; donor-specific antibodies

INTRODUCTION

Antibody-mediated rejection has been recognized as the leading cause of graft dysfunction and graft loss after kidney transplant. Antibodies against the human leukocyte antigen play a major role in this process, thus making it a critical barrier for solid organ transplantation. Precise and timely detection of human leukocyte antigen (HLA) donor-specific antibodies (DSAs) is vital for evaluating humoral immune status of patients pre- and posttransplantation. According to the occurrence time and type of immune response, HLA-DSAs are distributed into three groups: 1. HLA-DSAs identified before kidney transplant (preformed HLA-DSAs) can cause early rejection, such as hyperacute rejection, accelerated acute rejection, early acute antibody-mediated rejection, and graft loss; 2. *de novo* HLA-DSAs developed after transplant are associated with late acute antibody-mediated rejection, chronic antibody-mediated rejection, and transplant glomerulopathy; 3. "benign" HLA-DSAs are not considered clinically relevant because they are not associated with antibody-mediated rejection and graft loss [1].

The technology of screening antibodies has advanced from the complement-dependent cytotoxicity assay, enzyme-linked immunosorbent assay, to multiplexed particle-based flow cytometry (Luminex) – a qualitative microbead-based immunoassay for the detection of both class I and II IgG anti-HLA antibodies. Single antigen beads are used to characterize the preformed HLA-DSAs before transplant as well as any *de novo* development of HLA-DSAs after transplant [2, 3].

Current transplant practices recommend against offering a kidney from the donor expressing an unacceptable HLA antigen (positive virtual crossmatch). Only the patients whose HLA antibodies are not donor-directed will appear on the match run (negative virtual crossmatch).

The development of de novo HLA-DSAs after kidney transplant was reported in 13–30% of previously nonsensitized patients. The risk factors for *de novo* HLA-DSAs include the following: 1) high HLA mismatches (especially DQ

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mismatches), 2) inadequate immunosuppression and nonadherence, and 3) graft inflammation, which can increase graft immunogenicity. *De novo* HLA-DSAs are predominantly directed to donor HLA class II mismatches and usually occur during the first year of kidney transplant but can appear at any time, even several years later. HLA-DSA binding to antigen expressed on allograft endothelial cells can activate the classic complement pathway, a key pathological process of acute antibody-mediated rejection phenotypes [1]. Some HLA-DSAs can cause graft damage through antibody-dependent cellular cytotoxicity and induce subclinical and chronic antibody-mediated rejection phenotypes. Furthermore, HLA-DSAs can cause graft injury by direct activation of endothelial proliferation and consequent development of transplant glomerulopathy and vasculopathy.

According to the World Health Organization (WHO), adherence to long-term therapy is defined as the degree to which the person's behavior corresponds with the agreed recommendations from a responsible health care provider (physician, nurse) with regard to the type and dosage of drugs, dietary regimen, daily habits, and work–life balance. Nonadherence is quite common after kidney transplant, occurring in about 22% of patients (reported prevalence rates range 8–55% in some transplant centers) [4, 5, 6]. Intentional nonadherence is manifested by deliberate modification of treatment recommendations by the patient, such as irregular or improper taking of prescribed medication (e.g. omission on weekends or holidays, skipping the dose, taking lower or higher doses than prescribed, changing dosing intervals, consuming drugs at an improper time of the day, taking the wrong drug, complete discontinuance of the therapy). Nonadherence also includes nonattendance at scheduled control examinations, avoiding or rejecting laboratory appointments. Risk factors for noncompliant behavior of the patient after kidney transplant can be attributed to the patient themself, transplant center, or therapy regimen. Patient-related factors can pertain to age, sex, renal transplantation without a previous period on dialysis, education level, socioeconomic factors, taking psychoactive substances, and history of previous nonadherence with other therapeutic procedures. Factors associated with the transplant center include inadequate pre- and posttransplant education, poor communication and lack of confidence in the transplant team, and period after the transplantation procedure. Potential lack of cooperation between patient and health care provider may be attributed to the therapeutic regimens implicating a wide range of diverse drugs, adverse effects of drugs, as well as high medication costs.

It is important to differentiate adherence from compliance. According to WHO, adherence requires the patient's commitment and active participation in the treatment, relying on good communication between the patient and health care provider as the prerequisite for a successful clinical course. Contrary to that, compliance represents a passive following of medical advice, where the patient is regarded as an object and solely a recipient of care [4].

Besides other factors associated with graft loss, such as glomerulonephritis, polyoma virus nephropathy, medical/surgical conditions, antibody-mediated rejection is responsible for graft loss in more than 50% of cases (64% of cases). Within this sample population, a high percentage (47%) was associated with the *de novo* formation of DSAs due to nonadherence [6]. Accordingly, *de novo* DSAs are associated with a significant reduction in 10-year graft survival *vs.* in the no *de novo* DSA group [7].

The aim of this study was to describe the association between nonadherence and *de novo* DSA formation with consequent rejection and permanent loss of kidney transplant function.

CASE REPORT

The patient was subjected to chronic hemodialysis in December 2016, with chronic tubulointerstitial nephritis as the most probable underlying cause of end-stage renal disease (kidney biopsy was not performed since the disease had been diagnosed at a highly advanced stage). In October 2017, the 21-year-old patient underwent kidney transplant from a living-related donor with a matching blood type. HLA typing revealed one mismatch at the HLA-B and one in HLA-DR loci (MM 2/6) with a negative final crossmatch with fresh serum from the recipient and lymphocytes from the donor (CDC). Induction therapy included a monoclonal antibody [IL-2 receptor blocker (basiliximab (Simulect, Novartis Pharma AG, Basel, Switzerland), 20 mg on days 1 and 4)] and methylprednisolone (750 mg; 10 mg/kg body weight). Tacrolimus, mycophenolate mofetil, and prednisone were used as immunosuppressive maintenance therapy. Serum samples from the recipient were analyzed for class I and class II IgG HLA antibodies using a qualitative microbead-based immunoassay based on a Luminex platform. The presence of donor-specific class I and class II IgG HLA antibodies was confirmed neither six months nor one month before (prospective) as well as 15 days after the transplant procedure. Also, complement-dependent cytotoxicity (CDC) assay performed one month before transplantation did not reveal the presence of class I and class II HLA-DSAs.

Immediate postoperative course at the Department for Transplant Surgery was uneventful, without complications and with a gradual decrease of serum creatinine levels (value at discharge from hospital: creatinine = 110 μmol/L), satisfactory diuresis, while ultrasonographic examination revealed normal graft morphology and patency of vascular structures. Low levels of tacrolimus (2.3 ng/mL) were observed at the regular outpatient control examination performed three months posttransplant (January 2018) followed by gradual increase of serum creatinine levels, which reached twice its initial value after five months (in March 2018). The patient was hospitalized and underwent additional examination to identify the reasons for graft function impairment. The following results were obtained: negative urine and blood BK virus DNA PCR, negative cytomegalovirus DNA PCR, and hemolytic uremic syndrome was excluded. Qualitative detection of IgG antibodies in recipient's serum revealed the presence of class I and class II

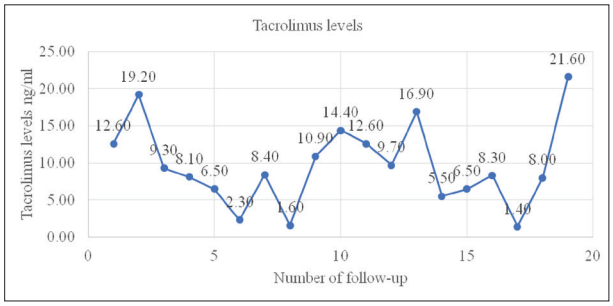

Figure 1. Tacrolimus levels during follow-up

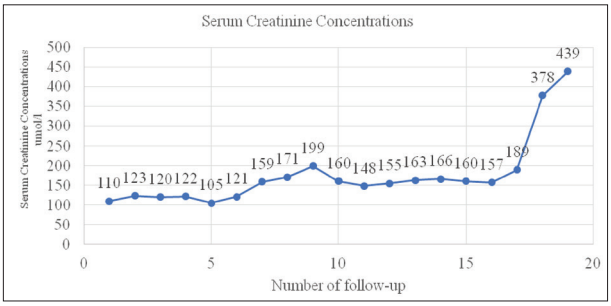

Figure 2. Serum creatinine concentrations during follow-up

HLA-DSAs, with very high anti-HLA-DQB1*06 antibody titer and mean fluorescence intensity (MFI) values being anti-HLA-DQB106:01 MFI = 21,446, 06:02 MFI = 19,870, 06:03 MFI = 20,507, 06:04 MFI = 20,725. It was confirmed that anti-HLA-DQB106:04 antibody was a donor-specific *de novo* formed antibody (supplementary high-resolution HLA typing confirmed that the donor was a DQB106:04 carrier). Acute antibody-mediated rejection of kidney transplant was diagnosed and treated with corticosteroid pulses, immunoglobulins (total 50 g) combined alternately with five plasmapheresis sessions. The treatment resulted in gradual normalization of serum creatinine levels (maximum creatinine level was 226 μmol/L, creatinine level at the end of the therapy was 133 μmol/L). Monitoring of serum tacrolimus levels and dosage adjustment was performed. The dose of antihypertensive drugs was increased to stabilize arterial hypertension. Stable graft function persisted over the following one-year period, that is, until January 2019, when low tacrolimus levels (1.4 ng/mL), increase in serum creatinine, and proteinuria were detected again. Heteroanamnestic data indicated an irregular taking of immunosuppressive drugs as well as an inadequate hygiene-dietary regimen during Christmas and New Year holidays. Repeated HLA-DSAs testing revealed the presence of class I and class II anti-HLA-DQB1 IgG antibodies, yet with significantly lower MFI values as compared to those recorded in March 2018 (anti-HLA-DQB1*06:04 MFI = 5933). Percutaneous graft biopsy was performed. Histopathological analysis revealed morphologic changes in all nephron components, C4d-positive staining in < 10% of peritubular capillaries, chronic active antibody-mediated rejection (2b), acute T-cell-mediated rejection (Banff grade IA), interstitial fibrosis, and tubular atrophy (I) according to the Banff classification. Corticosteroid pulses, immunoglobulins (0.5 g/kg body mass), and five plasmapheresis sessions were prescribed. The treatment did not result in the desired therapeutic response; thus, total graft loss occurred (Figures 1 and 2).

Ethics: Before the start of the study, approval was granted by the Ethics Committee of the University Clinical Center of Vojvodina, Novi Sad, Serbia (No.: 00-281). Written informed consent was obtained from the patient to publish this case report.

DISCUSSION

As far back as some 30 years ago, the age of the patient was considered to play an important role in nonadherence after renal transplant. Relative risk for adherence to medical recommendations in patients over 50 and younger than 20 was 1.564 and 0.800 (95% CI), respectively [8]. Moreover, kidney transplant from a living-related donor (as was the case in this article) is frequently reported as the reason for nonadherence, as compared with cadaveric transplantation. nonadherence occurs most commonly and is particularly pronounced during holiday seasons [9, 10, 11].

Nonadherence leads to suboptimal immunosuppression and consequent alloimmune activation and graft loss. Posttransplantation nonadherence to prescribed immunosuppressive regimen has been identified as an independent risk factor for unfavorable clinical course and a cause of 36% of kidney transplant losses [9]. Considering its importance and vital effects on immunosuppressive regimen, nonadherence is suggested to be regarded as the "fifth vital sign," which should be timely identified through regular monitoring of immunosuppressive drug levels (e.g. tacrolimus) and *de novo* formed DSAs. Problem identification and development of a personalized action plan with specific solutions (simplified medication regimen, education, and psychological behavioral support) are pivotal [12, 13, 14].

In the presented case, the unfavorable clinical course is to be attributed to nonadherence to recommended immunosuppressive regimen. Nonadherence has provoked suboptimal immunosuppression with consequent *de novo* formation of HLA-DSA and, most likely, primary antibody-mediated rejection. Continuous nonadherence further resulted in acute T-cell-mediated rejection with elements of chronic active antibody-mediated rejection and complete loss of function of the transplanted kidney.

Conflict of interest: None declared.

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Улога непридржавања терапије у настанку антитела специфичних за донора и њихов утицај на функцију трансплантираног бубрега

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САЖЕТАК

Увод Антителима посредовано одбацивање један је од водећих узрока губитка графта након трансплантације бубрега. Антитела специфична за донора (*DSA*) представљају један од биомаркера овог процеса, а циљ рада је био да прикаже улогу неадхеренције у њиховом настанку.

Приказ болесника Болеснику старом 21 годину, у октобру 2017. године, урађена је трансплантација бубрега од живог, сродног даваоца исте крвне групе, са једним неподударањем у *HLA-B* и *HLA-DR* локусу. Пре трансплантације није доказано присуство анти-*HLA* антитела специфичних за донора (*HLA-DSA*). Постоперациони ток је протекао без компликација. Три месеца након трансплантације запажен је низак ниво такролимуса, после чега је уследио пораст концентрације серумског креатинина. Пет месеци након трансплантације доказано је присуство *HLA-DSA*, са новостворeним антителом специфичним за донора, анти-*HLA-DQB*1*06:04, средњег интензитета флуоресценције (*mean fluorescence intensity – MFI*) од 20.725. Закључено је да се ради о акутном, антителима посредованом одбацивању трансплантираног бубрега, те је примењена следећа терапија: пулсна кортикостероидна терапија, имуноглобулини, плазмафереза. Стабилна функција графта одржана је наредних годину дана, када су се поново регистровали низак ниво такролимуса, пораст серумског креатинина и појава протеинурије. Хетероанамнестички су добијени подаци о нередовном узимању имуносупресивних лекова и неадекватном хигијенско-дијететском режиму живота. Поновљена анализа антитела анти-*HLA-DQB*1*06:04 показала је вредност *MFI* од 5933. Биопсијом графта нађени су елементи хроничног активног антителима посредованог одбацивања, акутног Т-ћелијама посредованог одбацивања, интерстицијалне фиброзе и тубуларне атрофије (класификација по Банфу). И поред поновљене терапије против одбацивања, дошло је до потпуног губитка функције графта.

Закључак Непридржавање препорученог имуносупресивног режима довело је до настанка *de novo HLA-DSA*, као и до развоја антителима и Т-ћелијама посредованог одбацивања, са последичним потпуним губитком функције трансплантираног бубрега.

Кључне речи: трансплантација бубрега; неадхеренција; антитела специфична за донора