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Significance of pretransplant and de novo anti-HLA antibody detection after simultaneous pancreas-kidney transplantation

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Abstract

Introduction. *Nowadays, there are few studies concerning assessment of the clinical significance of determining the level of pretransplant and de novo anti-HLA antibodies in patients after simultaneous pancreas-kidney transplantation.*

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Aim. *The study of the incidence, timing of formation and specificity of pretransplant and de novo anti-HLA antibodies in patients after simultaneous pancreas-kidney transplantation.*

Material and methods. *We conducted a prospective and retrospective research to study the incidence, timing of formation and specificity of pretransplant and de novo anti-HLA antibodies in 55 patients after simultaneous pancreas-kidney transplantation performed at the N.V. Sklifosovsky Research Institute for Emergency Medicine from 2008 to 2022.*

Results. *There were 4 patients with preformed anti-HLA antibodies (7%). The formation of de novo anti-HLA antibodies after simultaneous pancreas-kidney transplantation was observed in 17 patients (31%). There were 5 patients with anti-HLA class I, 3 patients with anti-HLA class II, 3 patients with anti-HLA class I and II, 5 patients with anti-MICA and 1 patient with both classes of anti-HLA and anti-MICA. The formation of de novo anti-HLA antibodies significantly increased the incidence of acute rejection (47% compared with 13%, p=0.014).*

Conclusion. *The frequency of pretransplant and de novo anti-HLA antibody detection in the recipients at our Center is comparable to published data from other transplant centers. We obtained evidence that the formation of de novo anti-HLA antibodies increases the incidence of acute rejection after simultaneous pancreas-kidney transplantation.*

Keywords: simultaneous pancreas-kidney transplantation, transplant immunology, de novo anti-HLA antibodies, pretransplant anti-HLA antibodies, acute rejection

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CVA – cerebrovascular accident
BMI - body mass index
CAPD - continuous ambulatory peritoneal dialysis
DM - diabetes mellitus
DSA - donor-specific antibodies
GCS - glucocorticosteroids
HD - hemodialysis
HLA - human leukocyte antigen
MHC - major histocompatibility complex - major histocompatibility complex
MICA - major histocompatibility complex class I chain-related gene A
MICB - major histocompatibility complex class I chain-related gene B
PDG - pancreaticoduodenal
PG - pancreas graft
PHD - program hemodialysis
RAG - renal allograft
RRT - renal replacement therapy
SPKT -simultaneous pancreas-kidney transplantation
TBI - traumatic brain injury

Introduction

Despite the recent improvement in graft and recipient survival rates after pancreas transplantation (PT) due to improvements in the perioperative management of patients and the immunosuppressive therapy protocols used, the incidence of a mid-term pancreas graft (PG) loss is still quite high [1]. Alloimmune sensitization after simultaneous pancreas-kidney transplantation (SPKT) is stronger than after isolated

kidney transplantation, due to the presence of a larger amount of immunogenic tissue (kidney graft tissue, exocrine and endocrine parts of the allogeneic pancreas parenchyma, segment of the donor duodenum) against a less degree of histocompatibility for HLA system antigens, for understandable organizational reasons [2–4]. Making diagnosis of pancreatic graft rejection is rather complicated, and with hyperglycemia detection at laboratory investigations, the damage to the pancreas, as a rule, is already irreversible [5]. To date, relatively few studies have been published on the impact of detecting elevated levels of antibodies to antigens of the human leukocyte antigen system (anti-HLA antibodies) on the outcomes of pancreas transplantation. According to some scientists, the results of the treatment of recipients with pretransplant anti-HLA antibodies are poored than those of non-sensitized patients, and the formation of de novo anti-HLA antibodies after transplantation increases the incidence of a graft loss [1–3, 6–9]. According to other investigators, the detection of anti-HLA antibodies does not statistically significantly affect the outcomes of pancreas transplantation, including of that in the form of simultaneous transplantation with kidney [10, 11].

Aim of the study was to investigate the rates and specificity of pretransplant anti-HLA antibodies, as well as the incidence, specificity, and timing of the synthesis of newly formed anti-HLA antibodies in patients after simultaneous pancreas-kidney transplantation.

Material and methods

We conducted a single-center study, in which we investigated the case rate and specificity of pretransplant anti-HLA antibodies, as well as the incidence, the timing of production, and the specificity of de novo donor-specific antibodies, assessed their direct impact on treatment outcomes in patients who underwent SPKT at the N.V. Sklifosovsky

Research Institute for Emergency Medicine in the period from 2008 to 2022.

Criteria for inclusion in the study were as follows:

- The presence of a "zero" point, that is, the determination of the level of anti-HLA antibodies before transplantation (n=74);
- A living patient with a functioning pancreaticoduodenal graft at the time of discharge from the hospital (n=59);
- A living patient at the time of the control study (n=57);
- The eligibility and consent to participate in the study (n=55).

Thus, of 79 patients who underwent SPKT in our center from 2008 to 2022, only 55 recipients met the inclusion criteria for the study.

The general characteristics of the studied recipients are presented in Table 1.

Table 1. Characteristics of the studied recipients

Age*, years	31 [31;39] (22;51)
Men/women n (%)/ n (%)	22 (40)/33 (60)
Blood type	
0(I), n (%)	20 (36)
A(II), n (%)	23 (42)
B(III), n (%)	11 (20)
AB(IV), n (%)	1 (2)
BMI*, kg/m^2	20.1 [19.2;22.5] (16.8;43.2)
Age of DM manifestation*, years	11 [7;14] (4;39)
Duration of DM*, years	24 [20;28] (4;39)
Duration of dialysis RRT DM*, years	2 [1;3] (0;10)
CAPD, n (%)	16 (29)
PHD, n (%)	36 (65)
Without HD, n (%)	3 (6)

Notes: *Me [25%;75%] (min;max), BMI – body mass index, DM – diabetes mellitus, RRT – renal replacement therapy, PHD – program hemodialysis, HD – hemodialysis, CARD – continuous ambulatory peritoneal dialysis

Allografts were obtained in the course of multiorgan harvesting from postmortem donors with ascertained brain death. Characteristics of posthumous donors are presented in Table. 2.

Table 2. Characteristics of donors

Age*, years	27 [23;32] (18;41)
Men/women n (%)/ n (%)	50 (91)/5 (9)
CVA /TBI n (%)/ n (%)	19 (35)/36 (65)
Serum creatinine*, μmol/L	96 [75;110] (50;180)
Blood urea*, mmol/L	4.9 [3.8;6.5] (1.4;9.3)

Note: *Me [25%;75%] (min;max), CVA − acute cerebrovascular accident, TBI − traumatic brain injury

The median preservation time for renal and pancreaticoduodenal grafts was 7.5 [5.5;9] hours and 9 [8;10] hours, respectively. Transplantations were characterized by a high degree of incompatibility for the HLA system antigens: the median percentage of incompatibility was I 100 [75;100]% for class, 100 [50;100]% for class II.

All patients received 3-component baseline immunosuppressive therapy (calcineurin inhibitors, mycophenolic acid drugs, corticosteroids) with induction by monoclonal or lymphocyte-depleting antibodies. The characteristics of the ongoing immunosuppressive therapy are presented in Table 3.

Table 3. Characteristics of immunosuppressive therapy

Induction immunosuppressive therapy	
Monoclonal antibodies (basiliximab), n (%)	44 (80)
Polyclonal antibodies, n (%) − ATGAM, n (%) − Thymoglobulin, n (%)	11 (20) 4(7) 7(13)
Baseline component of immunosuppressive therapy	
Calcineurin inhibitors: tacrolimus/cyclosporine, n (%)	53 (96)/2 (4)

HLA typing and detection of anti-HLA antibodies

Prior to transplantation, donors and recipients were typed with antigens of the main histocompatibility complex of class I (loci A and B) and class II (locus DRUB). Polymerase chain reaction by the method of specific oligonucleotides (SSO) was used for DNA typing using the Lifecodes HLA SSO Typing Kit on the Luminex platform (Immucor, USA). In the "donor-recipient" pair, incompatibility was determined for the HLA-A, HLA-B, HLA-DRB 1 antigens in an amount from 0 to 2 in each allele or in an amount from 0 to 6 in total for all alleles.

In recipients, when placed on the waiting list, anti-HLA antibodies against classes I and II, as well as MICA were determined using LABScreen kits (ONE LAMBDA, USA) on the Luminex platform (xMAP technology). The data of the studies were expressed as mean fluorescence intensity (MFI). At MFI values less than 500 c.u. the result was assessed as negative. After SPKT, the presence of antibodies was assessed on days 15–22 in a planned manner, or earlier in case of a suspected rejection. In addition, in the long-term period, the level of antibodies was determined at 6 and 12 months after transplantation. The control study was made from 15.07.2021 to 06.12.2021, its timing varied from 14 days to 12.3 years after SPKT , the median timing was 7.3 [1.9; 9.2] years. Subsequently, the level of anti-HLA antibodies was determined in the event of significant clinical manifestations, such as a graft rejection or the addition of infectious complications. Pretransplant anti-HLA antibodies and those formed de novo in the post-transplant period were identified. The anti-HLA antibodies detected before transplantation were considered pretransplant ones, de novo anti-HLA antibodies were defined the anti-HLA antibodies that were absent before transplantation, but appeared after SPKT , as well as pretransplant anti-HLA antibodies which level increased after transplantation by more than 10% of the baseline. De novo anti-HLA antibodies formed in the post-

transplant period, but not detected during the control study, were referred to as "transient". De novo anti-HLA antibodies formed after transplantation and detected during the control study were referred to as "persistent".

Depending on the identification of de novo anti-HLA antibodies, the patients were divided into two groups. Group I consisted of patients who did not develop de novo anti-HLA antibodies, group II included the patients with anti-HLA antibodies identified de novo. The recipients of both groups were comparable in terms of the main factors (see Table 4).

Table 4. Characteristics of Group I and Group II Patients

Factor	Group I (n=38)	Group II (n=17)	p*
Recipients			
Age**, years	34 [31;38.8] (26;51)	33 [31;38] (22;40)	0.523
Men/women, n (%)/n (%)	15 (40)/23 (60)	7 (41)/10 (59)	0.567
Blood type 0(I), n (%) A(II), n (%) B(III), n (%) AB(IV), n (%)	 16 (42) 14 (37) 7 (18) 13)	 4 (23.5) 9 (53) 4 (23.5) 0 (0)	 0.154 0.205 0.460 0.691
BMI**, kg/m^2	20.2 [19.3;21.7] (16.8;43.2)	20.1 [19.3;23.2] (16.9;25.7)	0.809
Age of DM manifestation**, years	11.5 [8,3;14] (5;35)	9 [7;13] (3;16)	0.116
Duration of DM**, years	22 [20;27.8] (4;39)	25 [21;28] (18;32)	0.371
Duration of RRT**, years	2 [1;3] (0;10)	2 [1;4] (0;10)	0.873
Donors			
Age**, years	28.5 [24;32] (19;38)	25 [23;29] (18;41)	0.196
Men/women, n (%)/n (%)	36 (95)/2 (5)	14 (82)/3 (18)	0.165
CVA/TBI, n (%)/n (%)	15 (40)/23 (60)	4 (24)/13 (76)	0.201
Serum creatinine**, μmol/L	92.6 [75;109] (50;155)	101 [82;113] (59;180)	0.358
Blood urea**, mmol/L	4.7 [3.8;6.5] (1.4;9.3)	5.4 [4;6.7] (2.9;9)	0.278
SPKT			
Miss-match I***, %	100 [75;100]	100 [75;100]	0.1 34
Miss-match II***, %	100 [50;100]	100 [50;100]	0.6 35
RAG preservation**, hours	7.3 [6;9.8] (1.5;14)	7.5 [5.5;8.5] (3.5;10)	0.572
PDG preservation**, hours	9 [8;10] (6;12)	9 [8.10.5] (6.5;12.5)	0.750
Immunosuppressive therapy			
Tacrolimus/cyclosporine, n (%)/n (%)	36 (95)/2 (5)	17(100)/0(0)	0.473
Monoclonal/polyclonal antibodies, n (%)/ n (%)	29 (76)/9 (24)	15 (88)/2 (12)	0.262

Notes: * Fisher's exact test for qualitative features, Mann-Whitney test for quantitative ones; **Me [25%;75%] (min;max); ***Me [25%;75%]; RAG – renal allograft; PDG − pancreaticoduodenal graft

Early postoperative period was considered the first 3 months or 90 days after SPKT; long-term period was that of over 3 months or 90 days after SPKT.

Statistical data processing

Statistical data processing was carried out using statistical programming in R language. Comparison by quantitative characteristics was carried out using the Mann–Whitney U-test. The impact of a qualitative binary variable on an outcome was assessed using Fisher's exact test. Differences were considered statistically significant at $p<0.05$.

Results

Pretransplant anti- HLA antibodies

The presence of pretransplant anti-HLA antibodies was detected in only 4 patients (7%). Anti-HLA antibodies to only class I antigens were detected in 2 of them, to only class II antigens in 1 patient. In one more case, the presence of anti-HLA antibodies to classes I and II antigens were detected. The remaining recipients had no antibodies to MHC (major histocompatibility complex) antigens detected before transplantation. In the post-transplant period, anti-HLA antibodies were not detected in one of those 4 patients during the control study and during the entire follow-up period. In 3 recipients in the early post-transplantation period (10^{th}, 7^{th} and 17^{th} days of the postoperative period), an increase in the pretransplant level of anti-HLA antibodies was observed. In 2 cases, a multiple increase in the titer of anti-HLA antibodies was seen, which in one recipient was accompanied by the development of an acute renal graft rejection of the vascular cell type, (Banff severity category 2B), which required a combined anti-crisis therapy: pulse therapy with glucocorticosteroids (GCS) and the administration of lymphocyte-depleting antibodies. At the time of the

control (follow-up) study, all of these recipients showed satisfactory function of both transplanted organs.

Newly formed anti- HLA antibodies (de novo anti-HLA antibodies)

The production of de novo anti-HLA antibodies in the post-transplant period was noted in 17 patients (group II). The specificity of antibodies is shown in the Figure.

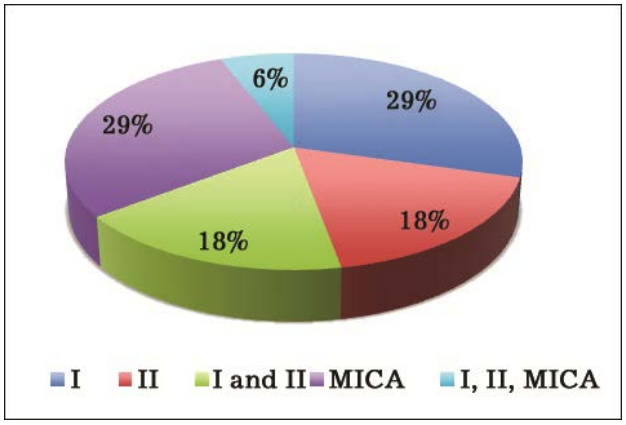

Figure. Distribution of patients depending on the specificity of de novo anti-HLA antibodies

De novo anti-HLA antibodies were "transient" in 8 recipients, and "persistent" in 4; in 5 patients they were determined only during the control study.

In the early postoperative period, the appearance of de novo anti-HLA antibodies were observed in 8 patients on days 7–32 after SPKT, the median timing of their detection was 16.5 [10;22] days., De novo anti-HLA antibodies detected were to class I antigens in 3 patients, to class II antigens in 2 patients to, to antigens of both HLA classes in other 3 patients. In the long-term period, de novo anti-HLA antibodies were detected in 9 patients within 2.9 to 8.9 years, the median timing was 6.1[3.8;7.8] years. De novo anti-HLA antibodies to class I antigens developed in 2 patients; to class II antigens- in one patient; to antigens of

the MICA class in 5 patients; to antigens of all three classes (I, II, and MICA) in one patient.

The incidence and timing of the rejection development

The development of an immunological conflict (a rejection reaction) was noted in 13 of 55 patients (24%). Most of the patients who underwent the rejection were from group II (n=8.61%), the smaller part represented group I (n=5.39%). The rejection incidence in group II recipients (n=8.47%) was statistically significantly higher compared to that in group I recipients (n=5.13%) (p=0.014).

In patients with newly detected (de novo) anti-HLA antibodies in the early postoperative period, 4 episodes of rejection occurred. In 3 cases, the RAG acute rejection was diagnosed (on the 7^{th}, 10^{th}, and 14^{th} days); in another case, there was an acute rejection of the pancreaticoduodenal graft (on the 13^{th} postoperative day). All episodes of rejection were successfully controlled: one patient with RAG rejection received pulse therapy with corticosteroids with a favourable clinical effect; in 3 other cases, a combined anti-crisis therapy (pulse therapy with corticosteroids and administration of polyclonal antithymocyte antibodies) was performed.

Patients with detected de novo anti-HLA antibodies at a later stage after SPKT (n=9) did not show any laboratory and/or clinical signs of an active rejection at the time of detecting antibodies. However, we should note that 4 recipients had previously experienced episodes of the acute rejection in the early postoperative period. Thus, one recipient with detected de novo anti-HLA antibodies of class II had previously experienced an episode of acute RAG rejection on postoperative day 17. Also, 1 female patient with detected de novo anti-HLA antibodies to class I had previously developed an episode of an acute PDG rejection on the 20^{th} postoperative day. In two cases, the patients with subsequent

detection of anti-MICA antibodies had been diagnosed with the following in the early post-transplant period: an acute rejection of PDG on the 25th postoperative day in one case; a concurrent rejection of RAG and PDG on the 5th day of the post-transplantation period in the other case. In one patient with an acute RAG rejection, the GCS pulse therapy proved to be effective; in the second recipient with a RAG rejection, and in a patient with a PDG rejection, the rejection reaction was successfully stopped by GCS pulse therapy followed by infusions of lymphocyte-depleting polyclonal antithymocyte antibodies. In the case of a concurrent RAG and PDG rejection, the anti-crisis therapy included a steroid pulse therapy, polyclonal antibody infusions, and three plasmapheresis sessions. At the time of the control study, the PDG was no longer functioning in 2 patients from this subgroup, and the patients were receiving insulin therapy.

In 5 patients of group I, the early postoperative period was complicated by am acute rejection development. One patient developed an acute isolated rejection of PDG on the 35^{th} day of the postoperative period, two patients developed an acute isolated rejection of RAG on the 15^{th} and 51^{st} days after transplantation. In 2 cases, an acute rejection of both grafts was observed on the 19^{th} and 37^{th} postoperative days. In 4 patients, the crisis was stopped by pulse therapy with corticosteroids in a total dosage of 1000-1250 mg. Only in one case, a combined anti-crisis therapy was required that included 10 injections of lymphocyte-depleting antibodies and 3 plasmapheresis sessions.

The development of an immunological conflict is one of the common causes of a pancreaticoduodenal graft loss. In literature, there are many reports on the impact of de novo-formed antibodies against major histocompatibility complex antigens on the outcomes of transplantation of organs such as kidney, liver, and heart. However, there has been still a relatively small number of studies on the impact of both

pretransplant and de novo anti-HLA antibodies on the outcomes of pancreas transplantation. In our country, the results of such studies have not yet been published at all.

As a result of our study, we obtained data comparable with the data published by other authors [1–3, 5, 6]. Thus, pretransplant anti-HLA antibodies were found in 4 patients of 55 (7%). We should note that de novo anti-HLA antibodies were found to be formed in 3 of them in the post-transplant period. In no case did we observe the loss of grafts that were functioning adequately at the time of the control study. The formation of de novo anti-HLA antibodies was noted in 17 patients (31%), in 8 of whom the early postoperative period was complicated by an acute rejection crisis development: a RAG rejection in 4 patients, PDG rejection in 3 patients, and a combined PAT and PDT rejection in one. Of particular interest is the identification of de novo antibodies against MICA-antigens in 5 patients. MICA-specific antibodies were detected at 3–8 years after SPKT. In 2 cases, the formation of anti-MICA antibodies was observed in patients who had the episodes of PDG rejection in the early post-transplant period, which resulted in the loss of pancreaticoduodenal complex function in one case. The MIC genes, which name originates from MHC Class I chain-related genes, the chain associated with MHC (major histocompatibility complex) class I genes, were discovered in 1994. They are located on the 6th chromosome in the region of the HLA genes of Class I B-locus [12, 13]. Seven MIC gene loci are known, of which MICA (more than 60 allelic variants) and MICB (about 25) have the highest polymorphism. The products of the MICA and MICB genes are involved in the immune response, provide costimulation of NK cells and T lymphocytes, and are present on the surface of epithelial cells, keratinocytes, and monocytes [12, 13]. MICA antigens are among the most significant non-HLA antigens that induce antibody formation and may affect a transplantation outcome. Clinical

studies have shown that anti-MICA antibodies are associated with an increased rejection rate and reduced graft survival of allogeneic kidney and heart, and are also associated with the chronic lung rejection development [12]. Thus, we assume that, in addition to anti-HLA antibodies, the outcome of pancreas transplantation may be influenced by the formation of de novo antibodies against MICA antigens, which should be taken into account in case of the graft dysfunction development at 3–8 years after organ transplantation. However, this conclusion certainly requires further studies.

The detection of de novo anti-HLA antibodies in patients statistically significantly correlates with an increased incidence of the rejection of transplanted organs. Thus, the rejection rate was 13% (n=5) in group I, and 47% (n=8) in group II (p=0.014). The performed anti-crisis therapy demonstrated a high efficacy: none of the recipients lost the function of transplanted organs in the early postoperative period. However, in 2 recipients, at 2.8 and 6.9 years after transplantation, we observed a loss of pancreaticoduodenal graft function, which was probably due to immunological causes. Examination showed an elevated level of anti-MICA antibodies (MFI=16368) in one recipient and an increased level of anti-HLA antibodies to class II antigens (MFI=1850) in another recipient. This, in turn, confirms the importance of determining the content of anti-HLA antibodies before transplantation, and of regularly monitoring the level of de novo anti-HLA antibodies after it. This applies both to the early postoperative period, and to their routine annual determination in the uncomplicated course of the post-transplant period; or, more often, with the development of significant clinical manifestations, such as rejection of grafts or the associated infectious complications.

Conclusions

1. The case rate of pretransplant anti-HLA antibodies after simultaneous pancreas-kidney transplantation was 7% (n=4).

2. The incidence of de novo formation of anti-HLA antibodies after simultaneous pancreas-kidney transplantation was 31% (n=17).

3. Anti-HLA antibodies to class I antigens were formed in 5 patients de novo, to class II antigens in 3 patients, to HLA class I and II antigens in 3 patients, anti-MICA antibodies in 5 patients, and both HLA classes and anti-MICA antibodies in 1 patient.

4. De novo formation of anti-HLA antibodies accompanied a statistically significantly higher rate of an acute rejection (47% vs. 13%, p=0.014).

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