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Utility of Protocol Pancreas Biopsies for De Novo Donor-specific Antibodies

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Anti-HLA donor-specific antibody (DSA) is an important biomarker for predicting graft injury and failure.[1] The appearance of DSA against the HLA, which can now be measured accurately and repetitively, is routinely monitored and managed in posttransplant recipients with positive outcomes of early diagnosis of subclinical rejection. Percutaneous pancreas allograft biopsy has been the gold standard for many decades to assess the etiology of pancreatic injury and determine the type and severity of rejection.[2] It is considered relatively safe and yields a diagnostic to help guide therapy. In recipients of various solid organ transplants, the monitoring of posttransplant DSA followed by protocol biopsy for the detection of de novo DSA (dnDSA) may result in improved outcomes through the early diagnosis of subclinical rejection. Even among pancreas transplant recipients (PTRs), the detection of dnDSA posttransplant has been associated with inferior graft survival.[3] Previously, Uva et al noted a 47% rate (7 of 15 patients) of subclinical rejection of either kidney or pancreas allograft in pancreas and pancreas-kidney recipients where allograft biopsy was performed 1 to 17 mo after dnDSA detection in the setting of stable and normal graft function (ie, normal pancreatic enzymes, normal blood glucose, and stable creatinine).[4]

At our center, we recently protocolized routine monitoring of posttransplant DSA in all PTRs followed by protocol biopsy after the detection of dnDSA. Posttransplant DSA monitoring is performed at 6 mo, at 12 mo, and thereafter annually in all PTRs. Among PTRs with calculated panel reactive antibodies >0, DSA is checked at 6 wks and 3 mo posttransplant. Recipients with pretransplant DSA receive additional DSA monitoring at 3 wks posttransplant. DSAs are detected pre- and posttransplant using Luminex single antigen beads (One Lambda, Canoga Park, CA) performed according to the manufacturer's instructions, except a reduced volume of beads (3 versus 5 μL) is used. In our program, we do not rely on strict mean fluorescence intensity (MFI) cutoffs to assign HLA antibody specificities. Instead, antibodies are identified using multiple criteria, including patterns of epitope reactivity, MFI value, specific-bead behaviors, and assay background, as described previously.[5] All positive specificities had MFI values above 300. DSAs are classified as dnDSAs if they appeared after transplantation and were not detected in pretransplant samples. Because pretransplant antibodies did not need to meet a minimum MFI threshold to be "identified," any antibody defined as "dnDSA" in this study is less likely to be due to increases in weak pretransplant DSA than in studies that use MFI thresholds. The strength of dnDSAs is represented as the sum of the MFI value (MFI_{sum}) of all DSA.

A total of 9 PTRs, 4 SPKs and 5 PTAs, underwent protocol pancreas biopsy for dnDSA, all in the presence of normal pancreatic enzymes and stable renal and glycemic parameters. The basic demographics and outcomes of these PTRs are presented in Table 1. Of these, 2 PTRs, both PTAs, had subclinical T cell–mediated rejection, and 2 additional PTAs had indeterminate pancreas rejection. 3 PTRs had dnDSA against class I antigen only and 3 against class II antigen only, and 3 had a mixture of both class I and II. The most common dnDSA specificities were against DQ and DR, each in 4 PTRs. Both PTA recipients with subclinical rejection had functional grafts at last follow-up, which was >2 and 5 y postbiopsy, respectively. Among the 4 SPK recipients, none had pancreas rejection; however, 2 had subclinical kidney antibody-mediated rejection. Only 1 PTR, patient number 9, had 2 more subsequent biopsies after index biopsy for dnDSA, both due to a rise in pancreatic enzymes, and both were negative for rejections. None of the remaining 8 PTRs had risen in pancreatic enzymes or had subsequent biopsies. Discordant rejection finding is a common phenomenon with kidney rejection being more common in SPK recipients.[6] Also, there could be a substantial incidence of discordant rejections with the presence of pancreas rejection only, as an experience from our institution among 40 SPK recipients has shown. We reported 25 recipients with concordance for rejections or no rejection, whereas in the remaining 15, there was discordance in the organ affected with 10 having only pancreas rejection and 5 having kidney only rejection.[7] Not only that, in the same study, we noted even among those with concordance for the presence of rejection, there was a clinically meaningful rate of finding different types or severity of rejection in the

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TABLE 1.

Basic demographics and outcomes

Pt no.	Age at Tx (y)	Sex	Types of Tx	Interval from Tx to dnDSA (mo)	dnDSA loci	MFI of each dnDSA loci	Sum dnDSA MFI	Immunos around time of dnDSA	Interval from dnDSA to panc biopsy (mo)	Panc biopsy findings	Panc C4d staining	Management after dnDSA/Bx	Interval from dnDSA to last follow-up (mo)	Panc outcomes
1	32.4	F	SPK	47.3	DQ6	3384	3384	Tacro + MMF + pred	2.9	No rejection	<1%	Treatment of kidney subclinical rejection with IVIG + Dex + rituximab	61.7	Functional graft, not on antidiabetic agent.
2	40.2	M	PTA	0.23	B57 DQ6	1491 2377	3868	Tacro + MMF + pred	0.56	TCMR II	20%	IVIG + Dex	68.4	Functional graft, not on antidiabetic agent.
3	48.5	F	PTA	1.2	A24	521	521	Tacro + MMF	2.5	No rejection	C4d neg	No change	87.7	Functional graft, not on antidiabetic agent.
4	34.9	M	SPK	0.46	A32	15478	15478	Tacro + MMF + pred	0.7	No rejection	C4d neg	No change	86.7	Functional graft, on low dose insulin.
5	34.0	M	PTA	4.46	A2 B70 Cw10	471 1018 1221	2710	Tacro + MMF + pred	0.96	Indeterminate for TCMR	C4d neg	No change	48.6	Functional graft, not on antidiabetic agent.
6	39.5	M	SPK	3.7	B13 B61 Cw15 DR7 DR15 DR53 DR51 DQ2 DP1 DP17	2738 991 982 3615 2178 2625 4149 8697 6818 4288	37081	Tacro + MMF + pred	4.2	Neg for rejection	C4d neg	No change Kidney biopsy neg for rejection but pyelonephritis	46.1	Functional graft, not on antidiabetic agent.
7	28.1	F	PTA	12.7	A29 B27 DR53 DQ2 DQ5 DQ5	1818 555 583 9033 6907 5251	24147	Tacro + MMF	0.46	TCMR II	C4d neg	ATG + Dex + IVIG	24.4	Functional graft, not on antidiabetic agent.
8	53.4	M	SPK	0.8	DR13 DR52	7759 1451	9210	Tacro + MMF + pred	0.6	Neg for rejection	C4d <1%	Kidney rejection treated with steriod + IVIG + Ritux	35.4	Functional graft, not on antidiabetic agent.
9	43.8	M	PTA		DR7	1384	1384	Tacro + MMF + pred	0.13	Inderminate for TCMR	C4d 1%	No change	8.6	Functional graft, not on antidiabetic agent.

dnDSA, de novo donor-specific antibody; IVIG, intravenous immunoglobulin; MFI, mean fluorescence intensity; MMF, mycophenolate mofetil; TCMR, T-cell medicated rejection.

2 organs.[7] Similarly, findings of the high rate of discordance in rejection were reported previously by Troxell et al.[8] Although limited by small sample size, our data support the possible utility of serial DSA monitoring followed by protocol biopsy for dnDSA despite stable graft function among PTRs, similar to other solid organ transplants,[9,10] while always balancing risk versus benefit in clinical decision making.

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