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A common antidonor reactive serological pattern in patients with failed kidney regrafts

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Abstract. Twenty retransplant patients were serially screened for donor-reactive antibodies (DRA). DRA appeared exclusively in patients whose grafts permanently failed and these DRA shared some common features, namely early appearance (days 4-8 post-transplant), high titers (1:10 up to more than 1:400), and broad anti-HLA specificity. This preliminary data would suggest that regrafted patients with primary graft failure represent a distinct subgroup of particularly immune responsive individuals.

Key words: Kidney transplantation - Retransplantation - Monitoring - Donor-reactive antibodies.

Graft outcomes of 517 transplantations done in GDR transplantation centers have revealed an extremely high incidence (45.5%) of permanently nonfunctioning donor kidneys in regrafted recipients in contrast to the relatively low rate (19.5%) of primary graft failure in first transplant patients [1]. These results suggest that patients who need to be regrafted are at high risk, due to a restimulation of humoral immunoeffectors primed by the first graft and/or to a distinct response pattern in individual patients. Perdue [2] recently concluded from the results of an extensive analysis of UCLA Registry data on risk factors for second transplants that subsets of patients show different antidonor reactivity patterns and that this distinctly different response behavior probably exists prior to any challenge by transplantation.

In the present study we tried to detect a common serological response pattern in repeat transplant patients whose grafts failed permanently after transplantation. (Only one patient, no. 970, had primary graft function but this failed on day 2 and could not be reversed.)

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Patients and methods

Our analysis comprised 100 patients for whom frozen donor spleen lymphocytes were available. Eighty patients received a first cadaver kidney and 20 patients were regrafted. All prospective recipients were carefully selected excluding the mismatched antigens of the first donor. Pre- and post-transplant sera of all patients were retrospectively screened for donor-reactive antibodies using the standard NIH microcytoxicity test with nonseparated frozen spleen lymphocytes as targets.

Results

Donor-reactive complement-dependent lymphocytotoxic antibodies (DRA) were found in the post-transplant sera of 9 out of the 20 (45.2%) regrafted patients as compared to 10 out of the 80 (15.3%) first cadaver kidney recipients. This difference is statistically significant (Chi-square test $P<0.001$, $n=100$). Subdividing both groups into those pa-

Table 1. Appearance of donor-reactive antibodies (DRA) in first transplant and retransplanted patients with or without graft function

	Function	DRA		
		+	−	
First transplants	Yes	3	32	NS
	No	7	38	
Retransplants	Yes	0	10	$P<0.001$
	No	9	1	

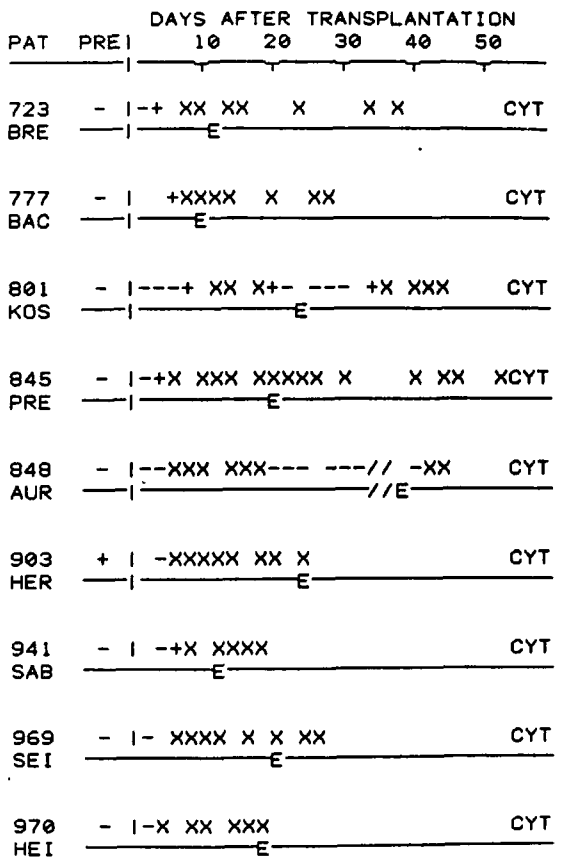

Fig. 1. Pre- and post-transplant follow-up of donor-reactive antibodies (DRA) in nine regrafted patients with primary graft failure showing a common reactivity pattern in all cases. *CYT* Microcytotoxicity test, + weak reaction (40-60% dead test cells), *X* strong reaction (60-100% dead test cells), - negative reaction, *E* time of graftectomy

tients whose grafts never functioned and those whose did, the following results were obtained (Table 1): (1) within the first transplant group, no difference could be found between the two subgroups regarding the number of DRA-positive patients; (2) in the regrafted group, none of the patients with functioning grafts was found to have DRA, while 9 out of 10 (90.0%) patients with permanently failing grafts proved to be DRA-positive after transplantation (Chi-square test, $P<0.001$, $n=20$).

To further characterize the nine DRA-positive patients in the retransplant group we studied the time of first appearance of DRA (Fig. 1). Surprisingly, DRA behaved similarly in all patients, appearing between days 4 and 8 post-transplant and, as a rule, persisting during the entire follow-up period. In our retrospective analysis, one patient (no. 902) showed weak cytotoxic activity pretransplant but was negative at the time of immediate pretransplant crossmatching using fresh lymph node lymphocytes. All DRA-positive sera proved to be highly titered (1:10 up to more than 1:400) and showed broad anti-HLA reactivity patterns against a selected lymphocyte panel (unpublished data). With regard to the pretransplant state of presensitization (maximum and actual panel reactivity) and HLA-mismatches (Table 2), we found no statistically significant differences between the two regrafted groups.

Figure 2 shows the results of follow-up of DRA in first transplant recipients. All patients were crossmatch-negative immediately before transplantation.

Table 2. Presensitization and HLA-mismatches in retransplant patients with nonfunctioning and functioning grafts. PRA max, Maximum panel reactivity; PRA act, actual panel reactivity

Patient	Function	PRA max	PRA act	Mismatch AB:DR	Mismatched antigens				DRA
723	No	85	35	2:0	A12	A32			Yes
762	No	15	6	2:0	B35	B37			No
777	No	10	0	2:0	A24	B51			Yes
801	No	40	0	2:1	A1	B8	DR3		Yes
845	No	20	20	2:1	A24	B40	DR3		Yes
848	No	50	30	1:1	A3	DR6			Yes
903	No	60	20	2:1	A2	B51	DR4		Yes
941	No	60	55	3:1	A30	A31	B18	DR3	Yes
969	No	0	0	3:0	A2	A32	B27		Yes
970	No	0	0	1:0	A31				Yes
738	Yes	93	0	2:0	A3	A30			No
771	Yes	46	0	1:0	B13				No
931	Yes	90	85	1:1	A2	DR3			No
940	Yes	60	5	2:1	A1	B37			No
943	Yes	15	0	2:0	A11	B7			No
958	Yes	0	0	2:1	A24	B15	DR5		No
962	Yes	13	0	2:0	A25	B15			No
986	Yes	0	0	1:0	A9				No
992	Yes	55	10	2:0	A1	B18			No
1007	Yes	10	0	3:0	A2	A3	B35		No

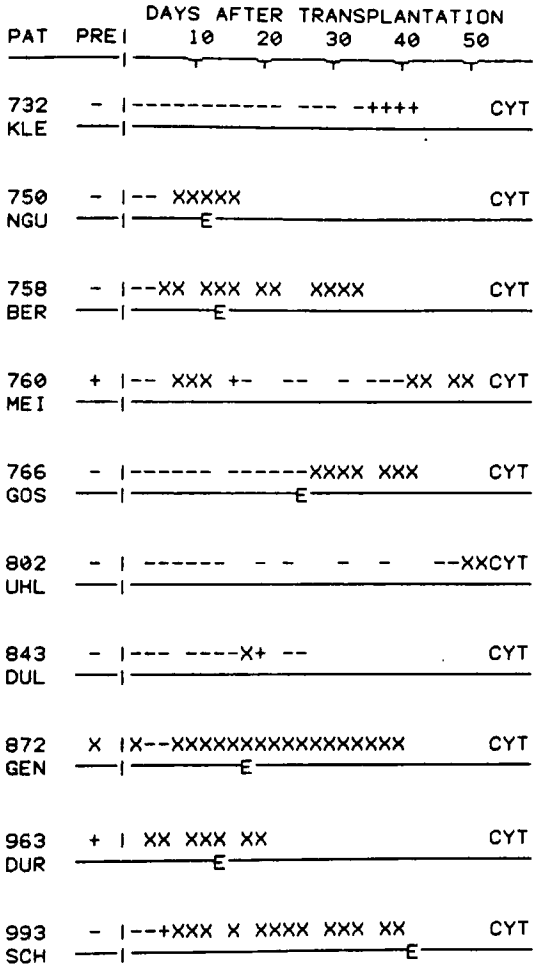

Fig. 2. Pre- and post-transplant follow-up of donor-reactive antibodies (DRA) in ten first transplant patients. One patient (no. 843) had primary function, one patient (no. 732) had delayed function, and the remainder had primary graft failure (abbreviations as in Fig. 1)

Only a few of the patients showed the kind of DRA patterns seen in failed regrafts. Half of them exhibited DRA titers of less than 1:2, but these were, in most cases, of broad anti-HLA specificity, as in the regrafted recipients.

Discussion

Our results suggest that regrafted patients with primary graft failure represent a distinct subgroup of particularly immune responsive individuals who share some common serological features. These features include the early appearance of DRA some days after transplantation, high titers (up to more than 1:400), and a broad anti-HLA reactivity. Our data appear to provide indirect evidence for an individual immune response pattern. What is now needed are tests to predict such individual immune response patterns in patients awaiting regrafts and to prevent primary graft failure in at least some regrafted patients.

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