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Renal transplantation with positive cross-matching test

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SUMMARY

Introduction: *Lymphocytotoxic antibodies reduce the expectancy of renal transplantation due to the increased risk of a positive crossmatch.*

Material and methods: *We analyzed the evolution of eight kidney transplants performed in our unit in presence of a positive crossmatch with historical T and/or B lymphocyte positive crossmatches.*

Results: *Mean panel reactivity was 76.6 ± 25.7 % (r: 22-100%), been higher than 75% in six patients. Six patients were recipients of a second or third transplant. Immunosuppression consisted of quadruple therapy including induction with thymoglobuline. Five patients had delayed graft function, and one had primary non-function of the graft. One patient lost her graft due to chronic allograft nephropathy in the second year postransplantation. Six patients maintained a good renal function (serum creatinine 1.2 ± 0.5 mg/dl, proteinuria 0.20 ± 0.34 g/day).*

Conclusion: *Renal transplantation in presence of a positive cross-match with historical serum and T lymphocytes and/or B lymphocytes, was followed by a satisfactory graft survival.*

Key words: ***Positive crossmatch. Renal transplantation. Sensitization. HLA-antibodies. Acute rejection. Induction therapy. Thymoglobuline.***

TRASPLANTE RENAL EN PRESENCIA DE UNA PRUEBA CRUZADA POSTIIVA

RESUMEN

Introducción: *La presencia de anticuerpos linfocitotóxicos reduce las expectativas de trasplante renal al incrementar el riesgo de presentar una prueba cruzada positiva con los potenciales donantes.*

Material y métodos: *Analizamos la evolución de los 8 pacientes trasplantados en nuestra unidad en presencia de una prueba cruzada positiva con linfocitos T con sueros históricos y /o linfocitos B.*

Resultados: *La tasa máxima de sensibilización fue de 76,6 ± 25,7% (r: 22-100%), siendo superior al 75% en seis pacientes. Seis pacientes eran receptores de un segundo o tercer trasplante. La inmunosupresión consistió en cuádruple terapia incluyendo inducción con timoglobulina. Cinco pacientes presentaron función retrasada del injerto y un paciente fallo primario del injerto. Un paciente presentó un episodio de rechazo agudo que respondió al tratamiento. Un injerto fracasó por nefropatía crónica en el segundo año de evolución. Los seis restantes mantienen una función renal adecuada (creatinina sérica 1,2 ± 0,5 mg/dl, proteinuria 0,20 ± 0,34 g/24 h).*

Conclusión: *El trasplante renal en presencia de una prueba cruzada positiva con linfocitos T con sueros históricos y/o linfocitos B, se siguió de unos resultados satisfactorios no debiendo constituir contraindicación para el trasplante.*

Palabras clave: ***Prueba cruzada positiva. Trasplante renal. Sensibilización HLA. Anticuerpos linfocitotóxicos. Inducción. Timoglobulina.***

INTRODUCCIÓN

The presence of lymphocytotoxic antibodies in serum of patients on the waiting list for renal transplantation limits patient's opportunities to achieve a successful transplantation.[1,2] The presence of these antibodies increases the risk for having a positive cross-matching test, which may contraindicate carrying out transplantation. It has been shown that patients with a high levels of lymphocytotoxic antibodies have greater incidence of delayed graft functioning and of acute rejection episodes, factors that have been related to shorter graft survival.[1,3-6] Since the implementation of cross-matching tests prior to transplantation, the positivity against donor's T lymphocytes and current recipient's serum is considered an absolute contraindication for transplantation, this not being the case with positive cross-matching with historical sera against T lymphocytes, or historical or current sera against B lymphocytes.[4,6-8] In parallel, the development in recent years of several immunosuppressive strategies has led to optimizing management of hypersensitized patients and carrying out transplantations that were historically contraindicated.[3] There are very few studies assessing the course of renal transplantations with positive cross-matching test in the intermediate-term.[5,9,10] We aimed at analyzing the course of renal transplantations with positive cross-matching tests performed at our Center.

MATERIAL AND METHODS

Population of analysis

We have carried out a retrospective analysis on the clinical course of 8 patients that received a renal transplantation with a positive cross-matching test (2.8%) from a total of 285 transplants done from November 1996 to January 2004. Mean follow-up time was 38.2 ± 28.2 months (range = 12-75 months). Demographic characteristics of patients are shown in Table I. Six patients (75%) were hypersensitized, considered as such those with a titer of lymphocytotoxic antibodies > 75%. The highest antibody titer was 76.6 ± 25.7% (range = 22-100%), and at the time of transplantation 43.8% ± 36.6% (range = 0-85%). All patients had previously been transfused, with an average number of transfusions of 14.7 ± 17.8 (range = 9-30). Mean time from inclusion into dialysis was 172.5 ± 67 months (range = 101.5-283.5). There were 4 male and 4 female patients, of which only one female patient had had two previous pregnancies. Two patients were candidate to their first transplant, and the remaining six were re-transplantations (four patients had received a previous graft, and two had received 2 previous grafts). The cause of graft loss with previous transplantations was early acute rejection in two cases, and chronic graft nephropathy in the remaining four.

Table I. Demographic characteristics of patients with incompatible cross-matching test

Characteristics	N = 8
Gender (M/F)	4 / 4
Mean age (years)	40.5 ± 13.8 (29 - 69)
Cause of renal failure (n):	
Glomerulonephritis	4
Lupus nephropathy	2
Interstitial	1
Unknown	1
Dialysis modality (n):	
Regular hemodialysis	5
Peritoneal dialysis + regular hemodialysis	3
Time on dialysis (months)	172.5 ± 67 (r: 101.5-283.5)
Pre-transplantation transfusions (n):	14.5 ± 7.8 (r: 9-30)
PRA maximum sensitization (%):	76.6 ± 25.7 (r: 22-100)
Last PRA sensitization (%)	40.8 ± 36.6 (r: 0-85)
HLA incompatibilities (n):	3.0 ± 0.7 (r: 2-4)
Time on cold ischemia (hours):	21.6 ± 4.5 (r: 15-28)

Cross-matching was done by means of the classical lymphocytotoxicity technique (NIH) at room temperature, based on determination of complement-fixing anti-HLA IgG antibodies with dithiothreitol (DTT) to rule out that positivity was due to the existence of autoantibodies. In cross-matching test, B and T lymphocytes from the donor were separately confronted to representative historical sera, including those with the maximal reactivity against the panel, and current recipient's sera. Cross-matching tests and titers of lymphocytotoxic antibodies are shown in Table I. HLA incompatibilities occurred in previous transplants were avoided in re-transplantations. Mean time between the most reactive serum and transplantation was 38.2 ± 55.1 months (range = 1.3-159.5).

Immunosuppressive protocol

It included anti-calcineurin agents (tacrolimus in 7 patients, starting dose 0.10-0.15 mg/kg/24 h, reaching target levels of 10-15 ng/mL, and cyclosporin microemulsion in one patient, at a starting dose of 10 mg/kg/day and target levels (C2) of 1800 ng/mL), combined to mofetil mycofenolate at an initial dose of 1 g/12 h, and prednisone according to the local

Table II. Results of cross-matching tests for lymphotoxicity (NIH) with DTT and maximum and pre-transplantation expression of lymphocytotoxic antibodies

Paatients (number)	T lymphocytes + historical sera	B lymphocytes + historial sera	B lymphocytes + current sera	Maximum level of lymphocytotoxic antibodies (%)	Last level of lymphocytotoxic antibodies (%)
1	0	1	1	80	0
2	1	1	1	100	75
3	0	1	1	60	40
4	1	1	1	76	76
5	0	1	0	22	0
6	1	1	0	85	0
7	1	1	0	100	75
8	0	1	1	90	85

(1: positive, 0: negative).

schedule. All patients received induction therapy with anti-lymphocyte globulins, according to historical availability of the Center, or OKT3 (5-7 doses). The first three patients of the series received ATGAM, (10 mg/kg/d), 4 patients received Thymoglobulin, (1.25 mg/kg/day) and one Ortoclone, (5 mg/day) because of a positive intradermal sensitivity test to globulins. All patients received anti-CMV prophylaxis with intravenous gancyclovir for 15 days, followed by p.o. gancyclovir until completing 3 months of therapy.

Grafts with delayed functioning were biopsied within the fifth day post-transplantation, similarly to those with renal function worsening without apparent cause or with suspected acute rejection.[11]

Analyzed variables

We assessed delayed graft functioning, need for hemodialysis and number of sessions received, incidence of acute rejection and histological severity, renal function by means of determination of serum creatinine levels and 24-h proteinuria and, finally, number of hospital re-admissions and their cause.

RESULTS

The number of administered globulin doses was 6.3 ± 0.9 (range = 5-7 doses). Five out of 8 patients (62.5%) had delayed graft functioning secondary to acute tubular necrosis confirmed by biopsy, 4 of them requiring dialysis therapy with an average of 5.0 ± 5.3 hemodialysis sessions (range = 1-11). One patient (number 6) had primary graft failure, with no evidence of acute rejection in further biopsies. One patient (number 3) with good initial graft functioning had acute rejection at day 9 post-transplantation, classified by means of biopsy as Banff's type II-B acute rejection. He received plasmapheresis therapy (5 sessions) and OKT3 (seven 5-mg doses). During the rejection period, the patient required two hemodialysis sessions, then having progressive renal function improvement with serum creatinine decrease down to 1.7 mg/mL, that remains stable to-date.

Mean serum creatinine for the 7 functioning transplants within 12 months of follow-up was 1.3 ± 0.5 mg/dL (range = 0.8-2.0) with proteinuria of 0.28 ± 0.39 g/24-h (range = 0-1) (Figures 1 and 2). There was a graft loss at 18 months post-transplantation (patient number 1) secondary to chronic graft nephropathy confirmed by biopsy in a female patient that received her first transplant for renal failure due to lupus nephropathy. The remaining 6 patients still have functioning grafts after a mean follow-up time of three years. They all have good renal function with average serum creatinine levels of 1.2 ± 0.5 mg/dL (range = 0.8-2.0) and proteinuria of 0.20 ± 0.34 g/24-h (range = 0-0.6).

Three patients (37.5%) were admitted to the hospital because of infectious complications, one patient because of acute appendicitis and urinary sepsis at month 6 from transplantation, and two others for acute cholecystitis and infection of vascular access for hemodialysis, respectively. All of them had satisfactory clinical course.

DISCUSSION

The group of sensitized patients represents 10-20% of the patients in the waiting list for first renal trans-

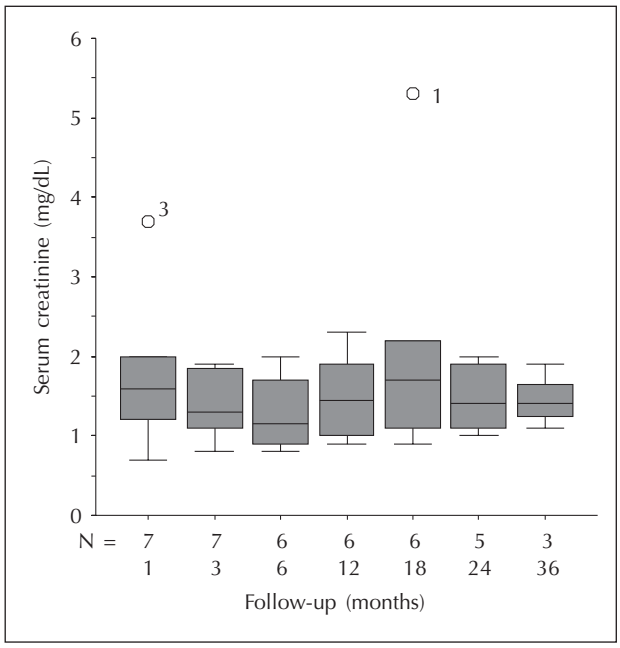

Fig. 1.—Course of serum creatinine levels in patients with preserved renal function (excluding the patient with primary graft failure).

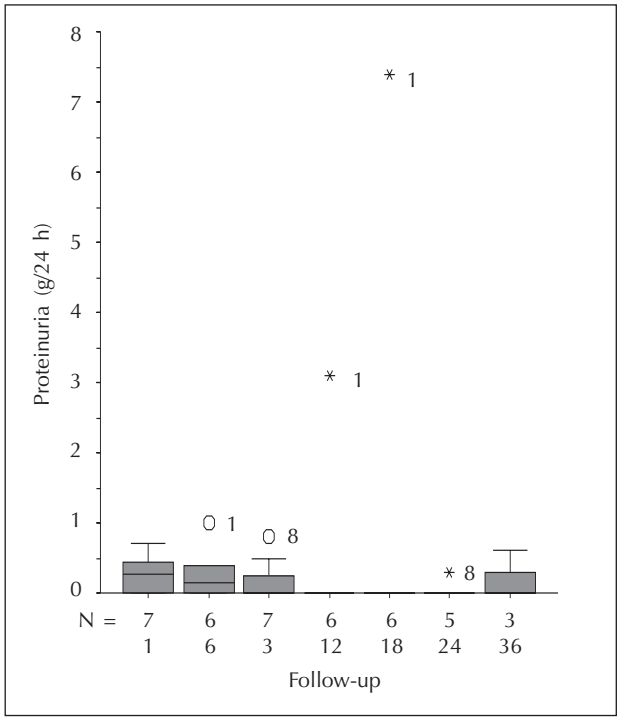

Fig. 2.—Average proteinuria levels in patients with functioning graft (excluding the patient with primary graft failure).

plantation, going up to 77% in case of re-transplantations.[1,12-14] In our country, the percentage of hypersensitized patients (antibody rate > 75%) represents 9.2% of the renal transplantation waiting list,[15] even being as high as 20-30% of the waiting list of other registries.[9,12,13] Among all patients that await a cadaver renal transplant, sensitized patients, and especially those hyperimmunized, are those that have the least likelihood of being offered a kidney due to positive cross-matching tests.[16]

The presence of lymphocytotoxic antibodies, as a result of transfusions, pregnancies, or previous renal transplants, increases the risk for a positive cross-matching test, and this risk increases as HLA-sensitization rates increase.[2,9,12] This limits the likelihood of receiving a renal transplant, these patients remaining in the waiting list 2.5-5 fold longer time than no-sensitized patients.[2,17] Besides, they present a greater risk of developing delayed graft functioning and humoral acute rejection, with the subsequent negative impact on graft survival.[1,12,17] A better prognosis has been described if hypersensitized patients receive high-compatibility grafts.[1,2,12]

Since 1960, cross-matching is routinely performed to rule out the presence of donor-specific lymphocytotoxic antibodies.[5] The pioneer technique was complement-dependent cytotoxicity (CDC) developed by Terasaki.[18,19] This tests allows for the detection of complement-fixing IgG antibodies against donor's class I HLA antigens (expressed on T and B lymphocytes) and responsible of hyperacute rejection.[5,7] However, the existence of cases with primary graft dysfunction due to hyperacute rejection with negative cross-matching tests done by this techinique[20] led to the development of more sensitive tests (AHG-CDC, ELISA, flow-cytometry, among others). These techniques allow for detection of complement-fixing and non-complement-fixing antibodies that might be implicated in early graft loss in those patients with increased risk for rejection, as re-transplanted and sensitized patients.[7,15,19,21,22]

It is assumed that a positive cross-matching test for T lymphocytes with sera obtained close to the time of transplantation in an absolute contraindication to transplantation;[8] however, the relevance of a positive cross-matching test with B lymphocytes with current and historical sera, in the presence of a compatible cross-matching with T lymphocytes is controversial.[5,6] There are studies that show a worse survival of renal transplant with a positive cross-matching with B lymphocytes as compared with those with a negative test,[23,24] although experiences in recent years with new immunosuppressive schedules do not find a worse graft survival in the intermediate-term.[5,22] In the same way,

the significance of a positive cross-matching test with T lymphocytes and historical sera is a matter of debate, provided that the test is negative with current serum.[4,6,7,8,25] A high incidence of delayed graft functioning is still observed, however,[6] the decrease in levels of lymphocytotoxic antibodies with time being a good prognosis factor in these transplantations.[4] In our series, we have included patients with positive cross-matching test with T and/or B lymphocytes provided that the test performed with T lymphocytes and sera from the last year would be negative.

Six out of 8 patients of the studied population had a maximum rate of anti-HLA antigen antibodies greater than 75% (76.6 ± 25.7; range = 22-100), all of them having received a high number of transfusions. Six patients had received previous transplantations, and in two, the underlying nephropathy was due to systemic lupus erythematous, an etiology that has been associated with a higher rate of lymphocytotoxic antibodies.[2] One patient had histological signs of cellular and vascular acute rejection that was reversed with plasmapheresis and OKT3 therapy. A second patient had primary graft failure with no evidence of acute rejection findings in post-transplantation biopsies. The finding of C4d deposition within the peritubular capillaries of the renal graft and detection of donor-specific antibodies post-transplantation confirmed the clinical suspicion of humoral rejection and initiating early therapy, increasing the likelihood for success.[26] However, in this case and the one having acute rejection the technique of C4d immunofluorescence was not performed, since it was not available at that time in our Center, and determination of donor-specific antibodies was not performed either, so that we could not rule out that failure would be due to humoral rejection.

Improvement of renal transplantation outcomes in patients with a positive cross-matching test is largely determined by advances in immunosuppression. In recent years, different protocols have been described aiming at decreasing immune response and preformed antibodies load that would allow for performing renal transplants with positive cross matching with good results. Baron *et al.* use anti-lymphocytic globulins for the first 10 days post-transplantation in sensitized patients that had a historical positive cross-matching test with T lymphocytes, with no differences being observed in serum creatinine, incidence of acute rejection, or two-year survival, as compared to patients with a negative test.[4] Akalin *et al.* observe good results in the short term in patients with a positive cross-matching test with the use of thymoglobulin for 5 days combined with 3 doses of intravenous immunoglobulins and triple therapy with cyclosporin.[5] Thibaudin *et al.* compare the efficacy of induction with anti-thymocytic globulin in patients with a maximum sensitization level of 40% and positive cross-matching test with B lymphocytes in 20% of the population, observing a lower incidence of acute rejection, a delayed onset of rejections, better renal function, and better graft survival than those patients not receiving such therapy.[3] Coupel *et al.* use induction with globulins, monoclonal antibodies, or anti-IL-2 antibodies for 7-14 days in second transplants, independently of the sensitization level, with good results in the short-term that the authors relate with a lower incidence of acute rejection episodes.[17] Dafoe *et al.* use OKT3 prophylactically in patients with positive cross-match observing a high rate of delayed graft functioning and lower incidence of acute rejection, which is delayed.[27] In isolated cases, preconditioning protocols have been used, which consist in different combinations, depending on the group, of hyperimmune globulin, plasmapheresis, immunoadsorption monoclonal anti-CD20 antibodies, or splenectomy and that have allowed performing transplantations with HLA- and AB0-incompatible living donor grafts.[28-30]

Finally, we should not forget that the development of waiting list preferential assignment techniques depending on the percentage of panel-positive antibodies, such as the national hyperimmunized plaque, still is, together with new immunosuppressive strategies, a valid tool that has increased the possibilities of transplantation in sensitized patients, with satisfactory outcomes.[16,31]

In patients from our series, we used anti-lymphocytic globulins and in one case OKT3, followed by a conventional immunosuppressant regimen. The incidence of delayed graft functioning was high, as described in the literature; however, the low incidence observed of acute rejection might have made evident the beneficial role of induction therapy in high immunological risk sensitized patients with some positive cross-matching test. The high level of clinical suspicion of and early biopsy taking allowed for early diagnosis and treatment of the acute rejection episode with a good response, although it may have been of interest to study the presence of C4d deposition in histological samples as well as donor-specific antibodies to rule out the existence of humoral rejection, both in this patient and in the one having primary graft rejection, as well as in the case of graft loss due to chronic graft nephropathy, given the role that humoral immune response may have in pathogenesis of the former.[33] As for the course of functioning grafts, and spite of the high incidence of acute tubular necrosis, all of them have had a good general course within three years of follow-up. Renal

function has remained stable through time with serum creatinine levels within the normal range, minimum proteinuria, and low mortality.

In our limited experience, renal transplantation in high immunological risk patients may be performed in the presence of a positive cross-matching test, with acceptable success expectations thanks to current immunosuppression protocols with no relevant side effects. Having a high degree of clinical suspicion before eventual complications would allow establishing early diagnosis and treatment, thus improving the outcomes.

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