Acute Antibody-Mediated Rejection in Kidney Transplant Based on the 2013 Banff Criteria: Single-Center Experience in Uruguay

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ABSTRACT

Background. Acute antibody-mediated rejection (AMR) diagnosis criteria have changed in recent consensus of Banff, with current evidence of C4d-negative AMR. Our objective was to evaluate incidence of AMR in renal transplantation according to Banff 2013 criteria and to examine the histological features and outcome.

Methods. This retrospective study involved all kidney transplants with histological diagnosis of acute rejection (AR) at our center between 2000 and 2014. All the biopsies with AR were re-assessed by a nephro-pathologist and classified by use of the Banff 2013 criteria.

Results. Of 205 kidney transplants, biopsy-proven AR was diagnosed in 25 cases (12%). Re-assessing them according to Banff 2013 criteria, AMR was diagnosed in 17 (8.3%) and represented 68% of the confirmed rejections. AMR diagnosis was performed on day 23 ± 26, with median of 11 days. From the 17 cases, 7 had concomitant T-cell–mediated rejection. All cases presented endothelial edema and acute tubular necrosis. Glomerulitis was found in 12 cases and capillaritis in 14. In 3, associated thrombotic micro-angiopathy (TMA) was found. Intimal and transmural arteritis was evidenced in 5 and 1 patient. In 2, transplant glomerulopathy was present. Seven of the 10 biopsies with C4d staining in the peri-tubular capillaries were positive. Twelve cases received plasmapheresis, 6 received gamma-globulin, and 6 received rituximab. After administration of anti-AMR therapy, 16 cases recovered renal function, reaching a serum creatinine level of 1.5 ± 0.6 mg %. Graft survival at 1 year was lower in the AMR group versus patients without AMR (81.9% vs 98.9%, log-rank test, $P < .001$). Risk factors for AMR were re-transplant (30% vs 7%, $P = .02$), HLA-DR mismatch (1.06 ± 0.65 vs 0.7 ± 0.6, $P = .03$), panel-reactive antibody (28% ± 33 vs 6.2 ± 13, $P = .00$), and delayed graft function (82% vs 30%, $P = .00$).

Conclusions. Adapting the new Banff 2013 criteria increased the sensitivity of the diagnosis of ARM. Regarding our data, despite an adequate response to the therapy, it resulted in a worse graft survival by the first year of renal transplant.

ACUTE ANTIBODY-MEDIATED REJECTION (AMR) is now recognized as a major problem in organ transplantation. AMR compromises graft outcome and frequently leads to graft loss [1,2]. On the basis of the initial Banff criteria, a definitive diagnosis of AMR required histologic, immunohistological (C4d deposition in peritubular capillaries), and serologic criteria (circulating donor-specific antibodies [DSA]). Such criteria were modified at the last Banff Consensus in 2013 to address the current evidence of the existence of C4d-negative AMR and lesions of intimal arteritis secondary to the action of the antibodies [3,4]. Our objective was to evaluate the incidence of AMR in our renal transplant population, as per the current criteria (Banff 2013), assessing the histological features as well as the course and prognosis of patients and graft.

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METHODS

This retrospective cohort study included all the episodes of acute rejection (both cell- and antibody-mediated) diagnosed on the basis of histology within the first 3 months after transplant. The patients were adults who had received kidney transplant at our center from 2000 to 2014. All of them were ABO-matched and had a negative specific donor micro-lymphocytotoxicity test at the time of transplant. Only the patients with more than 6 months of follow-up were included. Immunosuppression protocols included induction with anti-interleukin (IL)-2 monoclonal antibodies or polyclonal antibodies (rATG) and maintenance immunosuppression with cyclosporine or tacrolimus, mycophenolate, and steroids. All the renal biopsies were performed for delayed graft function (DGF) or acute impairment of renal function.

All the biopsies of patients with diagnosis of acute rejection were re-assessed by an independent nephro-pathologist who was unaware of the previous diagnosis and classified them by using the current criteria agreed at Banff 2013. The C4d staining had been available in Uruguay since 2010. The medical records were checked to obtain the demographic data and the therapy received. The analysis included potential risk factors for AMR, course, and graft survival at 1 year. DGF was defined as the need for dialysis during the first week.

Statistical Analysis

Values are expressed as absolute frequency and mean and median with interquartile range. Data analysis was performed with the use of the SPSS statistical package. The relation between two qualitative variables was assessed by applying the χ^2 test and Fisher exact test as appropriate. Multivariate logistic regression analysis was performed to identify independently significant factors in developing AMR. One-year graft survival was estimated by use of Kaplan-Meier survival analysis, and a log-rank test was used to compare survival curves. The significance value (P) was $\leq$.05. Written consent for data management was obtained at the moment of kidney transplant.

RESULTS

Of the 205 kidney transplants performed at our center during a 14-year period, biopsy-proven acute rejection was diagnosed in 25 cases (12%). R-assessing them according to Banff 2013 criteria, AMR was diagnosed in 17 (8.3%), and 8 cases (4, 8%) had T-cell–mediated acute rejection (TCAR) without evidence of AMR. The histological re-evaluation performed re-classified 2 previous TCAR without AMR to acute antibody-mediated rejection. AMR represented 68% of the histology-confirmed rejections.

Characteristics of AMR Cases (n = 17)

Mean age of patients with AMR was 42 ± 12 (range, 17–63) years; patients had been dialyzed for 66 ± 61 (range, 0–243) months before transplant. Nine patients were male. All except one underwent cadaveric donor transplantation. Four (0.3) were second transplants. Mean HLA-AB mismatch was 2.4 ± 0.87 and mean HLA-DR mismatch was 1.06 ± 0.65. Maximum pre-transplant peak panel-reactive antibody (PRA) was 28% ± 33% (range, 0–92) and cold ischemia time was 804 ± 367 min. Transplant induction therapy was administered to 13 of 17 (0, 7) patients: 4 received basiliximab and 9 rATG. Tacrolimus was used in 14 transplants and 3 received cyclosporine. All of them received MMF and steroids.

CLINICAL AND HISTOLOGICAL CHARACTERISTICS OF AMR

Diagnosis of AMR was performed histopathologically on day 23 ± 26 (2–86), with a median of 11 days. DGF was the indication of renal biopsy in 14 cases and in 3 cases for renal functional impairment. At the time of diagnosis, DSA were positive in 3 patients (17%) through micro-lymphocytotoxicity and in 6 (35%) through flow cytometry.

Regarding renal biopsies, from the 17 cases with diagnosis of AMR, in 7 cases concomitant T-cell–mediated rejection was found (0, 42) (Table 1). All the biopsies presented endothelial edema and acute tubular necrosis. Glomerulitis was found in 12 cases (0, 7), being graded as I in 5 cases and II and III in 5 and 2 cases, respectively. Capillaritis in the peritubular capillaries was found in 14 (0.8), graded I, II, and III, in 1, 2, and 11 patients, respectively. In 3 (0, 2) cases, there was associated TMA. Intimal and transmural arteritis was evidenced in 5 patients and 1 patient, respectively. In 2 patients, transplant glomerulopathy was already present. Seven of the 10 biopsies with C4d staining in the peri-tubular capillaries were positive (3 patients with C4d from 10% to 50% and 4 patients with peritubular capillaritis C4d >50%).

Therapy, Course, and Risk Factors for AMR

Therapy was started after receiving the histological diagnosis. Twelve (0, 7) AMR patients received plasmapheresis, with a mean number of 6.5 ± 3 sessions (range, 4–14); 6 (0, 35) received gamma-globulin (2 g/kg) and 6 (0, 35) rituximab with dosages of 820 ± 327 mg. Eleven (0, 65) patients also received rATG. After administering anti-AMR

Table 1. Histological Characteristics of AMR (n = 17)

Characteristic Value
Concomitant T-cell–mediated rejection, 42% (7)
Microvascular inflammation:
Glomerulitis, 70% (12)
• Grade I, 5
• Grade II, 5
• Grade II, 2
Peri-tubular capillaritis, 82% (14)
• Grade I, 1
• Grade II, 2
• Grade III, 11
Intimal or transmural arteritis, 35% (6)
Acute thrombotic micro-angiopathy, 17% (3)
Acute tubular injury, 100% (17)
C4d-staining CPT: 70% (7/10)
• 10% to 50%, 3
• >50%, 4
Transplant glomerulopathy, 11% (2)