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Acute vascular rejection: a clinical and morphological study

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Abstract We analyzed one special type of acute vascular rejection (AVR), defined as fibrous thickening of the arterial intimal layer that leads to early renal failure. Twenty-one patients who presented this histological pattern were studied among 339 transplanted over 4 years. Patients were separated into two groups. Thirteen patients have restained their kidneys (Group A, 61.9%) and 8 have lost their grafts (Group B, 38%). Diagnosis was made on average 430. POD in GA and at 49° POD in GB on the 43rd postoperative day in group A and on the 49th postoperative day in group B (NS). In group A, mean serum creatinine is 2.2 mg/dl and follow-up time is 29 months. Oliguria was much more frequent in group B (75% versus 15.3%, $P = 0.01$). These patients were submitted to 91 renal biopsies always because of non-function. Typical vascular lesions began at arcuate arteries and progressed, as seen in sequential biopsies, to interlobular arteries and arterioles. When only arcuate arteries were affected, 22.5% of renal losses were seen, but when arcuate plus interlobular arteries were compromised, 72.2% of patients lost their kidneys ($P = 0.006$). We did not identify any difference in immunofluorescent staining from biopsies with or without vascular rejection, or between groups A and B. We concluded that about 2.3% of our patients lost their kidneys because of this kind of AVR, diagnosed near the 43rd postoperative day. The only clinical predictive sign of poor reversibility was oliguria. The attack on arcuate plus interlobular arteries meant a poor prognosis. Immunofluorescent staining did not have a prognostic value.

Key words Kidney transplantation · Vascular rejection · Immunosuppression

Introduction

It is already known that most cellular rejections usually respond to methylprednisolone pulses, but rejections with intense vascular injury are associated with no response to steroids and a poor prognosis. In this paper, we report our results analyzing one special type of acute vascular rejection, called acute vasculopathy, defined as fibrous intimal thickening that leads to severe obliteration of the vascular lumen, and causes early and rapidly progressive renal failure. The immediate consequence of this disease is a reduction in renal blood flow and, therefore, acute tubular necrosis is universal, which causes progressive renal failure after transplantation. The majority of such grafts never reached an adequate function. Acute cellular rejection is also frequently seen in association with this intense vascular disease. We studied the patients compromised by this kind of rejection, which we called acute transplant vasculopathy, in order to find any prognostic features that could differentiate between those who restained the graft and those who lost the kidney.

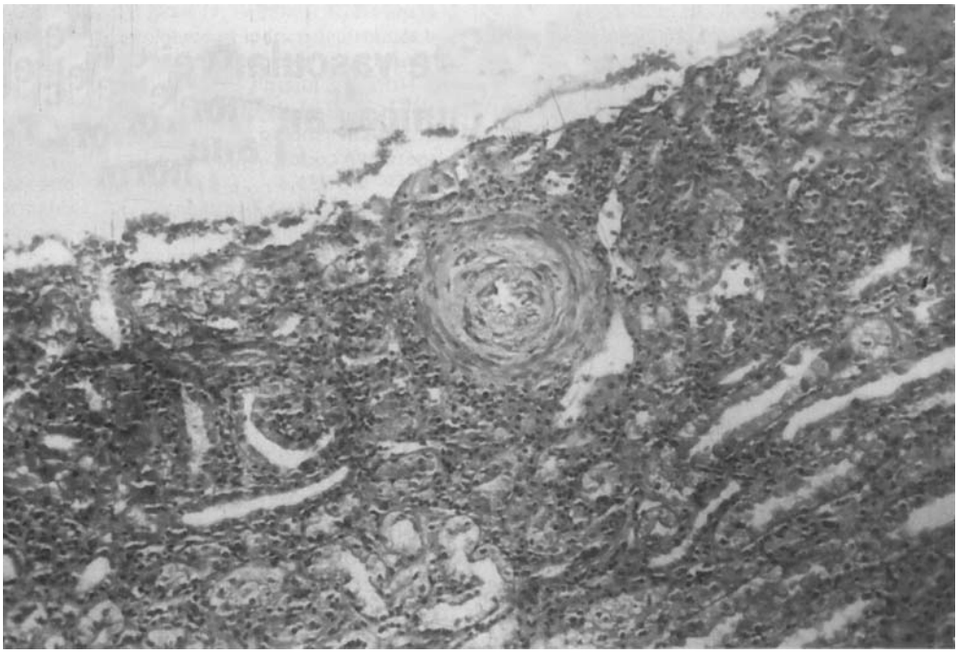

Fig. 1 Acute transplant vasculopathy (H&E; × 100)

Patients and methods

We analyzed 21 patients among the 339 transplanted (6%) over 4 years at our center who presented this histological pattern of acute transplant vasculopathy (Fig. 1) at, at least, one of the renal biopsies performed. Twelve patients were male and the mean age was 35.1 years (9–59). Eleven patients had chronic glomerulonephritis, 3 had diabetic nephropathy, 3 PKD, and 4 had undiagnosed nephropathies. Fourteen (52.6%) received cadaveric donor kidneys, 5 (39.6%) living related, and 2 (7.6%) living unrelated donor kidneys. Three were second transplants.

Acute transplant vasculopathy is considered to be a fibrous thickening of the arterial intimal layer that leads to severe obliteration of the vascular lumen. Some cases also presented mucoid edema, mononuclear cell infiltration, and fibrin in the subendothelial space. Immunofluorescence studies showed basically IgM and C3 in the intima. Acute tubulopathy was universal.

Results

Patients who presented at least one biopsy showing acute transplant vasculopathy were separated into two groups according to their outcome. Group A constituted 13 patients who retained their graft (61.9%) and group B 8 patients who lost their graft (38%). Sex, age, original disease, donor type, ABO typing, number of regrafts and transfusions before transplantation, and basic immunosuppression were similar in groups A and B. The number of acute rejection episodes and methylprednisolone pulses, monoclonal and polyclonal globulin courses (ten in group A, five in group B; NS), herpes virus infections, and dialysis requirement were also not statistically different. Diagnosis was made on average on the 43rd (range 17–178) postoperative day in group A and on the 49th (range 13–142) postoperative day in group B (NS). In group A, mean serum creatinine is 2.2 mg/dl (range 0.8–4), and follow-up time is 29 months. Oliguria was much more frequent in group B than in group A (75% vs 15.3%, $P = 0.01$). Lymphotoxicity tests performed before transplantation disclosed, in group A, one positive antiglobulin, DTT-negative T cell cross-match. In group B, one positive B cell cross-match was observed. After transplantation, we detected one positive T cell and two positive B cell cross-matches in group B. Sensitization was low in both groups, with panel-reactive antibodies lower than 5%. The highest panel observed after transplantation was 40% in a patient from group B. Results are summarized in Table 1.

These 21 patients were submitted to 91 renal biopsies, a mean of 4 histological studies per patient. Fifty-eight percent of them were percutaneous Tru-cut biopsies and 26 (28.5%) were surgically obtained. Seven (7.6%) were transplantectomy results. Considering only biopsies, 40% of them had no arcuate artery in the sample. There was no difference concerning the ability to obtain an arcuate artery in both biopsy methods, since percutaneous and surgical biopsies obtained the same number of arcuate arteries (53.4% versus 53.8%; NS), but only surgical biopsies were able to offer more than one arcuate artery per sample.

Typical vascular lesions began at arcuate arteries and progressed to interlobular arteries and finally to arteri-

Table 1 Clinical features and outcome of patients with acute transplant vasculopathy (*Cad* cadaveric, *LR* living related, *LNR* living not related, *ATG* antithymocyte globulin, *PRA* panel-reactive antibodies, *CM* cross-match, *ACR* acute cellular rejection, *MP* methylprednisolone, *IF* immunofluorescent staining, *POD* postoperative days)

Clinical features	Group A	Group B	
Number	12	9	NS
Gender (male/female)	7/5	5/4	NS
Donor: Cad	8	6	NS
LR	3	2	NS
LNR	1	1	NS
Retx	1	2	NS
Transfusions	7.1	8.5	NS
Dialysis need	8 (66.7%)	9 (100%)	NS
Immunosuppression	TR = 11; DL = 1	TR = 7; DL = 1; CL = 1	NS
Viral infection	5	1	NS
Age (years)	37.4	32.2	NS
ATG/OKT3 courses	10 (83.3%)	6 (66.6%)	NS
Follow-up time	29 months (4–55)	70 d (14–68)	–
Serum creatinine mg/dl	2.2	–	
CM before Tx	T AGH + DTT − = 1	B + = 1	
CM after Tx	–	T AGH + = 1 B + = 2	
PRA before Tx	< 5%	< 5%	
PRA after Tx	–	> 40%	
Results			
Diagnosis time	43.4 POD (17–178)	49 POD (13–142)	NS
Biopsies	2.9 (1–5)	2.8 (1–5)	NS
Oliguria	2 (16.6%)	6 (66.6%)	$P < 0.03$
Rejection episodes	3.5	2.3	$P < 0.02$
MP courses	2.5	1.6	$P < 0.03$
ACR present	7 (46.7%)	16 (69.5%)	NS
ACR absent	8 (53.3%)	7 (30.4%)	NS
IF positive	9 (52.9%)	13 (46.4%)	NS
IF negative	8 (47.0%)	15 (53.5%)	NS

oles, as could be seen by studying sequential biopsies. Diagnosis was made on average at the third renal biopsy in both groups, by the 40th postoperative day. Previous biopsies usually showed severe acute tubular injury, with no signs of epithelial regeneration, associated or not with acute lymphocytic infiltration. When only arcuate arteries were affected, we had 22.5% of renal losses, but when arcuate plus interlobular arteries were compromised, 72.2% of these patients lost their kidneys ($P = 0.006$). So, if one compares the damaged vessels in groups A and B, one can see that injury to arcuate plus interlobular arteries means a worse reversal rate of the rejection process.

In 58.5% of those biopsies, the vascular lesion was associated with mononuclear cells, but the course was similar for patients presenting mononuclear infiltrations or not. Twenty-three patients who had vascular rejection diagnosed, but with previous biopsies not showing this vascular lesion, were analyzed and 19 of them (82.6%) did not have any arcuate artery represented in previous histological studies, so we could not eliminate the possibility that the process had already begun, but had been misdiagnosed. In 4 instances, an arcuate artery was already present in previous samples, but no signs of vascular injury were seen (17.3%). Immunofluorescent staining could be analyzed in 44 instances and was negative 14 times, 7 of those in biopsies when acute transplant vasculopathy was diagnosed. Staining was positive in the mesangium and in the intimal arterial layer. We did not identify any difference between immunofluorescent staining from biopsies with or without vascular rejection or between patients from groups A and B.

Patients in group B lost their grafts, on average, at the 70th (range 14–168) postoperative day, even after intense immunosuppression. Group A had a mean follow-up time of 29 months and mean serum creatinine was 2.2 mg/dl. There was a statistical difference in the frequency of oliguria, which was much more frequent in the group that did not recover function. As a predictable consequence, group A, which presented a lower frequency of oliguria, had a higher number of diagnosed cellular rejection episodes and received more treatments with methylprednisolone pulses. A higher number of plasmocytes and neutrophils were seen in group B biopsies, which pointed to a worse prognosis, although this data was not statistically significant.

Discussion

Banff classification has been used to standardize nomenclature of the various histological pictures seen in transplant pathology. Solez et al. [3] classify vascular rejection into three grades: mild, moderate, and severe. The cases we describe in this paper correspond to grade 3 in the Banff classification.

Von Willebrand et al. [5] have noticed, like ourselves that rejections with vascular involvement are very heterogeneous concerning their outcome. There is a group that recovers function and a group that does not recover. In their experience, when acute cellular rejection is also seen, and when expression of IL-2R and HLA class II can be detected, the outcome is better. Otherwise, some vascular rejections are irreversible, mainly when neither cellular infiltrate nor upregulation of Il-2R and HLA-Dr are found. We were not able to detect any difference in the outcome between those vascular rejections accompanied by cellular infiltration and those free of infiltrate. We have to consider that treatment with steroids may be able to clean these infiltrates from biopsies while having no effect on the vascular disease.

Like our group, Demetris et al. [1] observed this kind of macrovascular rejection and called it "obliterative arteriopathy", an entity that was detected basically in the interlobar, arcuate, and interlobular arteries of the kidney. Van Saase et al. [4] also confirmed the relationship between vascular commitment and poor outcome, showing that early vascular rejection occurring within 3 months of transplantation is the most important predicting variable of both early and late graft losses. Pathogenic mechanisms involved in this kind of rejection are still poorly defined. Wang et al. [6] have studied the expression of plasminogen activator inhibitor 1 mRNA by an in situ hybridization technique and have found a strong expression in the endothelial cells of arteries and arterioles. This marker in kidneys indicated vascular, but not cellular rejection, which could be the reason for hemorrhage and infarcts.

Since those non-sensitized patients had this severe vascular rejection, we can speculate that a cellular immune-mediated mechanism is involved. Nevertheless, low titers of anti-HLA antibodies cannot be excluded. In this case, flow cytometry cross-matches should be able to predict which patients would present this troubled posttransplantation outcome. Humoral immunity may be of major importance in the pathogenesis of vascular rejection after kidney transplantation, and may explain the good responses described sometimes with plasma exchange. Franco et al. [2] have demonstrated good results using plasmaphoresis in patients presenting this acute endovasculitis, arriving at a 1-year graft survival rate of 60%. They proposed two mechanisms of action: either the removal of circulating lymphocytotoxic antibodies or the removal of some mediators of the lesion such as cytokines or immune complexes. Nevertheless, as also suggested by Yard et al. [7], the presence of antibodies directed against donor endothelial cells should also be considered as a pathogenic mechanism of acute vascular rejection. Further studies need to be done to clarify their role in this very severe type of vascular rejection.

References

1. Demetrius AJ, Zerbe T, Banner B (1989) Morphology of solid organ allograft arteriopathy: identification of proliferating intimal cell populations. Transplant Proc 21: 3667–3669
2. Franco A, Anaya F, Niembro E, Ahijado F, Luno J, Valderrabano F (1987) Plasma exchange in the treatment of vascular rejection. Relationship between histological changes and therapeutic response. Transplant Proc 19: 3661–3663
3. Solez K, Axelsen R, Benediktsson H, et al (1993) International standardization criteria for the histologic diagnosis of renal rejection: the Banff working classification of kidney transplant pathology. Kidney Int 44: 411–422
4. Van Saase JLCM, Van der Woude FJ, Thorogood J, Hollander AAMJ, Van Es LE, Weening JJ, Van Bockel JH, Bruijn JÁ (1995) The relation between acute vascular and interstitial renal allograft rejection and subsequent chronic rejection. Transplantation 59: 1280–1285
5. Von Willebrand E, Salmela K, Isoniemi H, Krogerus L, Taskinen E, Hayry P (1992) Induction of HLA class II antigen and interleukin 2 receptor expression in acute vascular rejection of human kidney allografts. Transplantation 53: 1077–1081
6. Wang Y, Thompson EM, Whawell AS, Fleming KA (1993). Expression and localization of plasminogen activator inhibitor 1 mRNA in transplant kidneys. J Pathol 160: 445–450
7. Yard B, Spruyt-Gerritse M, Claas F, Thorogood J, Bruijn JÁ, Paape ME, Stein SY, Van Es LA, Van Bockel JH, Koouymans-Coutinho M, Daha MR, Van der Woode FJ (1993) The clinical significance of allospecific antibodies against endothelial cells detected with an antibody-dependent cellular cytotoxicity assay for vascular rejection and graft loss after renal transplantation. Transplantation 55: 1287–1293