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Early and late urological complications corrected surgically following renal transplantation

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Summary

The purpose of this study was to assess outcomes of urological complications after kidney transplantation operation. Nine-hundred and sixty-five patients received a kidney transplant between 2000 and 2006. In total, 58 (6.01%) developed urological complications, including urinary leakage ($n = 15$, 1.55%), stenosis ($n = 29$, 3%), vesicoureteral reflux (VUR) ($n = 12$, 1.2%), calculi ($n = 1$, 0.1%) and parenchymal fistulae ($n = 1$, 0.1%). Urinary leakage cases were treated by ureteroneocystostomy (UNS) via a double-J stent and stenosis cases by UNS. Fenestration was performed in patients developing lymphoceles and unresponsive to percutaneous drainage. VUR treatment was performed by ureteroneocystostomy revision or UNS. Stent usage during ureteric reimplantation was observed to reduce urinary leakage. Surgical complication rates in renal transplantation recipients according to donor type (living versus cadaveric) and the status of stent use (with stent versus without stent) were 5.53% vs. 7.27% ($P = 0.064$) and 5.24% vs. 20% ($P < 0.01$) respectively. No recurrence, graft loss or death was seen after these interventions. Comparison of recipients with and without urological complication showed that there was no difference between groups ($P > 0.05$) with respect to last creatinine level. No graft or patient loss was associated with urological complications. Urological complications that can be surgically corrected should be aggressively treated by experienced surgeons and graft loss avoided.

Introduction

Urological complications after renal transplantations are one of the major causes of morbidity, delayed graft function, graft loss and patient mortality [1]. The majority of these are ureteral complications [2,3]. In the literature, urological complications such as leakage, stenosis and vesicoureteral reflux (VUR) are reported at a rate between 2.5% and 14.1% [4–7]. The most important factors contributing to occurrence of these complications include technical problems encountered during organ removal from the donor, its preparation and ureteral anastomosis [4,8]. It is recommended that excessive dissection of the site known as 'golden triangle' (the site confined by ureter, kidney and renal artery) be avoided, especially during organ removal, because it supplies nutrients for the ureter. It has been reported that necrosis of the distal ureter developed in 70% of cases with damage to this site [9]. Potential risk factors, including organ recipient's age, renal disorder, diabetes mellitus and prolonged cold ischemia, were reported not to play an important role in the occurrence of urinary complications [4]. We aimed to present the urological complications that were identified during the postoperative early and late periods and corrected by surgical interven-

tion in 965 cases after renal transplantation between June 2000 and September 2006 in our department.

Patients and methods

Patient files of 965 cases who received renal transplants from cadaveric or live donors in the Organ Transplantation Center, Akdeniz University School of Medicine, between June 2000 and September 2006 were retrospectively reviewed. Patients who developed postoperative early and late urinary complications after renal transplantation, including urinary leakage, stenosis, symptomatic VUR, calculi and parenchymal fistulae and were treated surgically were enrolled. Demographic data including patient and donor age, gender, etiology of chronic renal failure (CRF), type and duration of dialysis, duration of cold ischemia, tissue compatibility, surgical technique, urological complications requiring surgical treatment and treatment methods were assessed.

Standard method was used for organ harvesting from cadaveric donors and as transplantation technique. After performing open surgical method in 679 cases and laparoscopic method in 25 cases for organ harvesting from live donors, standard transplantation technique was used in the recipient. For the ureteric reimplantation technique, ureteroureterostomy (UU) was performed in 41 patients and ureteroneocystostomy (UNS) using Lich-Gregoir technique in 924 patients. Foley catheter and lodge drain were inserted in all patients during the operation. Double-J stent, which prior to 2003 was used only in selected cases, began to be used routinely in all patients thereafter, and was removed postoperatively at 2 or 3 weeks. Foley catheter was removed on postoperative day 1 in UU cases and on day 4 in UNS cases. Lodge drains were removed on postoperative days 1–5 based on the amount of the drainage.

Induction therapy of 2.5 mg/kg/day antithymocyte globulin (ATG) was used for transplantations from cadaveric donors. For renal transplantations from live donors, IL-2 receptor blockers (basiliximab or daclizumab) were used in selected cases (mismatch four and above) as induction therapy. Cyclosporine 6–8 mg/kg/day, tacrolimus 1.5–2 mg/kg/day, sirolimus 5–10 mg/day and everolimus 1.5–3 mg/day in combination with mycophenolate mofetil 1–2 g/day were used for the maintenance therapy in both groups. Steroid therapy initiated at a dose of 1 g in all patients during surgery was decreased to 20 mg/day at day 7. At the first 6 month period, our target trough levels for cyclosporine, tacrolimus, sirolimus and everolimus were 150–300, 8–12, 10–15 and 8–12 ng/ml respectively. After an additional 6 months, target trough levels for cyclosporine, tacrolimus, sirolimus and everolimus were 75–150, 3–7, 5–10 and 3–8 ng/ml respectively. Steroid pulse therapy (1 g/day) was given primarily during rejection episode. Polyclonal antibodies (ATG) were used for steroid-resistant acute rejection. Plasmapheresis was performed in selected cases with rejection in addition to anti-rejection therapy.

During the postoperative follow-up, urinary leakage was identified by the urine output, the amount of drained fluid, serum creatinine level, Doppler ultrasonography (USG) and scintigraphy (extravasation). Cases of stenosis associated with external pressure and intraluminary pathology were identified by the urine output, serum creatinine level, Doppler USG (pelvicaliceal dilation) and scintigraphy (prolongation and obstruction at excretion phase). Percutaneous drainage catheter was placed for symptomatic lymphocele causing obstruction symptoms and signs such as pelvicaliceal dilatation and creatinine increase. When the daily amount of lymphocele drainage was <10 ml, drainage catheter was withdrawn. If the percutaneous lymphocele drainage was unsuccessful and if symptomatic lymphocele recurred, we performed laparoscopic or surgical fenestration of lymphocele.

For cases with late stenosis at ureteric lower end identified by USG as having outflow obstruction, the diagnosis was confirmed primarily by percutaneous transplant nephrostomy followed by antegrade ureterogram. In intraluminary ureteric stenosis cases, fibrosis development at anastomosis site and/or intraluminary hemorrhage can cause urinary stasis. We did not perform dilatation operation percutaneously when urine flow was decreased. In all ureteric stenosis cases, we surgically corrected ureteric stenosis and at the same time we placed double-j stent. In our routine procedure in all ureteric stenosis cases, we prefer open surgical revision for definitive treatment.

For late follow-up, cases showing reflux (grade 3 or above) during voiding cystoureterographies performed after a febrile urinary tract infection, with three or more positive cultures along with elevated serum creatinine levels, and biopsy-proven reflux nephropathy cases were corrected by surgical reconstruction. Diagnosis was confirmed by USG and urinary spiral tomography in cases with symptomatic nephrolithiasis in the transplanted kidney.

Results

Renal transplantations from cadaveric donors ($n = 261$, 27.1%) and live donors ($n = 704$, 72.9%) were performed in 965 patients with CRF. Fifty-eight (6.01%) patients developed 47 urological complications treated surgically and 11 treated by percutaneous intervention. Among these 58 patients, 19 (32.75%) had renal transplants from cadaveric donors and 39 (67.25%) from live donors. CRF etiology included chronic glomerulonephritis ($n = 26$, 44.8%), unknown ($n = 15$, 25.8%), familial Mediterranean fever-amyloidosis ($n = 1$, 1.7%), diabetes mellitus ($n = 4$, 6.8%), hypertension ($n = 8$, 13.7%), calculi

Table 1. Demographic characteristics of the patients.

Characteristics	With urological complication ($n = 58$)	Without urological complication ($n = 907$)	*P*
Patient age	37.1 ± 10.6 (17–58)	34.4 ± 13.8 (6–73)	ns
Donor age	41.2 ± 15.7 (7–70)	42.0 ± 12.3 (5–72)	NS
Gender (M/F)	32/26	488/419	NS
Type of dialysis (HD*-PD†-Pre-emptive)	43-12-3	688-175-44	NS
Duration of dialysis	22.09 ± 26.5 (0–144)	26.5 ± 35.1 (0–216)	NS
Duration of cold ischemia (min)	233 ± 270 (30–840)	216 ± 184 (25–1380)	NS
HLA-mismatch, mean	3.5 ± 1.3 (0–6)	3.69 ± 1.44 (0–6)	NS
Duration of follow-up (month)	29.7 ± 19.8 (4–75)	27.8 ± 16.5 (0–75)	NS
Creatinine at discharge	1.4 ± 0.54 (0.5–3.6)	1.23 ± 0.6 (0.2–4.2)	NS
Final creatinine level	1.6 ± 0.8 (0.8–4.6)	1.72 ± 0.9 (0.4–4.9)	NS

*Hemodialysis; †Peritoneal dialysis; NS, non significant ($P > 0.05$).

($n = 1$, 1.7%) and VUR to native kidneys ($n = 3$, 5.1%). Comparison of demographic characteristics of the patients according to the presence or absence of urological complications are shown in Table 1.

Urinary leakage, which accounted for 25.8% of all urological complications, was observed in 15 patients (1.55%). All of these leakage cases [3 (5.17%) resulting from necrosis at lower end of the ureter and 12 (20.69%) from vesicoureteral anastomosis] developed during postoperative 15 days. Seven (46.66%) of these patients had double-J stent inserted during transplantation. All the leakage cases were treated by UNS revision with double-J stent. None of the cases had recurrence of anastomosis leakage. All urological complications are shown in Table 2.

Intraluminary and extraluminary stenoses, accounting for 50% of all urological complications, were observed in 29 (3%) patients. Of these stenosis cases, 10 (17.25%) resulted from intraluminary causes and 19 (32.75%) from extraluminary causes (Table 2). Extraluminary hematoma developed as a result of distal ureter bleeding into antireflux tunnel performed after UNS. Stenosis cases were treated as shown in Table 3.

Vesicoureteral reflux, which comprised 20.68% of the complications, was observed in 12 patients. Reflux cases with surgical indication were treated by UU or UNS revision based on the presence of reflux to receiver's native ureters (Table 3).

Surgery was planned in one patient who received a cadaveric transplant and was identified to have calculi leading to stenosis symptoms during the post-transplantation period. The symptoms resolved after the calculi passed during operational preparations.

Multiple percutaneous nephrostomy interventions were unsuccessful in a case with renal pelvicaliceal dilatation

Table 2. Complications after transplantation.

Complication	Number of patients ($n = 58$) *n* (%)	Complication rate ($n = 965$) (%)
Urinary leakage	15 (25.8)	1.55
Distal ureter necrosis	3 (5.17)	0.31
UNS leakage	12 (20.69)	1.24
Stenosis	29 (50)	3
Intraluminary	10 (17.25)	1.03
Ureteropelvic stenosis	2 (3.44)	0.2
Ureterovesical stenosis	3 (5.17)	0.31
Stenosis at UU line	3 (5.17)	0.31
Intraureteral hemorrhage	2 (3.44)	0.2
Extraluminary	19 (32.75)	1.96
Lymphocele	18 (31.03)	1.86
Hematoma	1 (1.72)	0.1
VUR	12 (20.68)	1.24
Calculi	1 (1.72)	0.1
Parenchymal fistula	1 (1.72)	0.1
Total	58	6.01

UNS, ureteroneocystostomy; UU, ureteroureterostomy; VUR, vesicoureteral reflux.

Table 3. Surgical treatment methods for complications after transplantation.

Complication (*n*)	Treatment (*n*)
Urinary leakage	
Distal ureter necrosis (3)	UNS revision (3)
UNS leakage (12)	UNS revision (12)
Stenosis	
Ureteropelvic stenosis (2)	Pyeloureterostomy (2)
Ureterovesical stenosis (3)	UNS revision (3)
Ureteral stenosis (3)	UNS (2), pyeloureterostomy (1)
Intraureteral hemorrhage (2)	Drainage (1), pyeloureterostomy (1)
Lymphocele (18)	Percutaneous drainage (18), fenestration (7)
Hematoma (1)	Surgical drainage
VUR (12)	UNS revision (5), UU or ureteropyelostomy (7)
Parenchymal fistula (1)	Open nephrostomy (1)

UNS, ureteroneocystostomy; UU, ureteroureterostomy; VUR, vesicoureteral reflux.

developing due to obstruction of pelvic hematoma that resulted as a complication of renal biopsy. In this case, urinary fistula developed from pelvis to incisional line after multiple nephrostomy interventions were performed. Thereafter, during operation, we drained the hematoma in the renal pelvis and placed double-J stent and nephrostomy catheter. When we determined closure of the fistula and open ureter in follow-up nephrostography 2 months after this operation, we removed the nephrostomy catheter which was placed in open-surgical operation.

We further analyzed the surgical complication rate according to donor type (living donor versus cadaveric donor) and the status of stent use (stent versus no stent). It was found that surgical complication rates in renal transplantation recipients according to donor type (living versus cadaveric) and the status of stent use (with stent versus without stent) were 5.53% vs. 7.27% ($P = 0.064$) and 5.24% vs. 20% ($P < 0.01$) respectively. Laparoscopic donor nephrectomy has been performed since the second half of 2006. We have not taken into account the complication rate in this group (to date, $n = 1$) because of the small number and because follow-up of this patient was very short.

No graft or patient loss was associated with urological complications. Comparison of recipients with and without urological complication determined that there was no difference between groups with respect to last creatinine level ($P > 0.05$). During long-term follow-up, two patients had graft loss due to biopsy-proven recurrence of primary kidney disease. Another patient died due to post-transplantation lymphoproliferative disease (PTLD).

Discussion

While the rate of urological complications after renal transplantation seems to be between 2.5% and 14.1%, it was 6.01% ($n = 58$) in our case series of 965 patients, consistent with the literature [4–7].

Urinary leakage, the most common complication during the early period, reportedly occurs at a rate of 0–8.9% [4]. The most frequent causes of urinary leakage are necrosis and suture failure due to vascular insufficiency [10]. In our series, urinary leakage was found in 15 cases (1.55%). Of these cases, three developed as a result of distal ureteral necrosis and 12 due to UNS leakage. Particular care should be given to preserving vascularization of the distal ureter during organ harvesting to prevent leakage due to ureteral necrosis. Also, during implantation of the ureter into the bladder, the ureter should be long enough and bending or rotation avoided to prevent necrosis. In the literature, double-J stent is not recommended due to its potential for increasing postoperative urinary system infections and its requirement of invasive intervention for its removal [11]. On the other hand, the use of double-J stent is recommended to support the anastomosis and to prevent bending or rotation of the ureter [6,12]. In our three cases with ureteral necrosis, entire-fold necrosis was present at a short segment of the lower end of the ureter; thus, we thought that it might be due to vascular insufficiency. While all 12 cases of urinary leakage were observed prior to 2003, during which period double-J stents were used only in selected patients, no leakage was seen after that year following the routine use of stenting. This supports the argument that routine use of double-J stent for UNS reduces urinary leakage, consistent with the study of Kumar *et al.* [6]. All cases with necrosis and leakage were treated by UNS revision with the use of double-J stent. No additional problems requiring surgical intervention occurred after the revision.

Stenosis is one of the major urological complications after transplantation. In the literature, stenosis was reported at a rate of 3.1–8% [13–15]. In our series, the incidence of stenosis was 3%. Ureteral stenosis might result from intraluminary factors such as calculi and a blood clot or extraluminary factors such as pressure exerted by blood and lymphatic fluid and also stricture at anastomosis line. In our study, we evaluated intraluminary causes in four groups (Table 2). We identified intraureteral hemorrhage in two cases (3.44%), and believed that intraluminary stenosis during the early postoperative period was due to horseshoe renal parenchymal transection in one and stent irritation in the other. We treated the case with horseshoe kidney by inserting double-J stent after drainage and the other by pyeloureterostomy because of the organized nature of hematoma in the latter. Three cases (5.17%) with ureterovesical stenosis were treated by UNS revision; two of the three cases (5.17%) with stenosis at UU line were treated by UNS revision and the other by pyeloureterostomy; and two patients with ureteropelvic stenosis (3.44%) were treated by pyeloureterostomy revision. Double-J stent was used routinely in all of these cases. Extraluminary causes of ureteral stenosis during the early postoperative period are lymphocele and hematoma. Lymphocele development, which occurred in 18 of our cases (1.86%), was reported at a similar rate, between 0.6% and 18%, in the literature [16]. Incomplete ligation of receiver's peri-iliac lymphatic network and renal hilus lymphatics exposed during donor's nephrectomy were implicated in lymphocele development [17,18]. We prefer ligation over cauterization during hilar dissection for donor's nephrectomy and minimal dissection of peri-iliac region and ligation of lymphatics during receiver's surgery to decrease lymphocele occurrence. For treatment of patients with symptomatic lymphocele, percutaneous drainage and laparoscopic or open peritoneal fenestration is preferred [17]. In cases presenting with obstruction

findings that showed lymphocele in USG, percutaneous drainage catheter was inserted primarily. Among seven patients with no regression of obstruction findings despite percutaneous drainage or with recurrence after withdrawal of drainage catheter, laparoscopic fenestration was performed in five and open peritoneal fenestration in two patients. In one of our cases, extraluminary stenosis due to bleeding underneath UNS tunnel was identified. During exploration, bleeding focus was ligated by creating a tunnel and a tunnel was reestablished.

One of the major causes of symptomatic urinary system infection and morbidity after transplantation is VUR. In the literature, VUR is reported to occur at a rate of 2–79% [19]. In our series, incidence of symptomatic VUR requiring surgical intervention was 1.24% ($n = 12$). The major causes of VUR in the implanted ureter are surgical reimplantation technique and the quality of the bladder wall. Most of the transplantation facilities prefer Lich-Gregoir or Politano-Leadbetter as the UNS method [20]. Both have their advantages and disadvantages. We preferred Lich-Gregoir technique, which is an effective method for prevention of VUR and has the advantage over the other technique in that operation time is short. During clinical follow-up, we identified 12 patients with symptomatic reflux and used UU or pyeloureterostomy for the treatment of patients without reflux into native ureters ($n = 7$) and UNS revision in patients with reflux into native ureters, and we corrected the condition surgically using stenting in both techniques. No graft or patient loss developed postoperatively. UU is also a surgical procedure performed in renal transplant recipients characterized by the absence of VUR into native kidney. It has an advantage to UNS procedure regarding VUR occurrence after renal transplantation, especially if UU is performed by an experienced surgeon [21]. UU or pyeloureterostomy revision might be preferred in cases with post-transplantation ureteral stenosis in addition to being an alternative treatment for complications such as reflux (Table 3). In contrast to the study of UU as the preferred primary post-transplantation procedure, no stenosis complication was observed in cases with UU as the secondary choice.

Among other urological complications, complications including urolithiasis and fistula in the transplanted kidney might be seen rarely. In the literature, the incidence of calculi in the upper urinary system is reported to be 0.23% in transplant patients [22]. In our series, there was one case (0.1%) with calculi in the upper urinary system. No graft loss was observed in 58 patients in whom urological complications after transplantation were treated surgically. Two patients operated for VUR during long-term follow-up developed graft loss due to recurrence of biopsy-proven primary disease (membranoproliferative glomerulonephritis). One of our cases surgically treated for leakage died from PTLD. Our results show that patients with urological complications have similar graft survival and last creatinine level to those of renal transplant recipients without urological complications, and confirm the studies reporting that patients with urological complications during long-term follow-up do not carry an additional risk for graft loss or mortality [4,15].

In an era with so limited a number of organ donors, transplanted organ and patient losses are seen, apart from inevitable factors including immunologic and infectious causes. Urological complications are the major cause of postoperative mortality and morbidity. Carefully employed surgical techniques to avoid urological complications during organ harvesting should decrease the incidence of these complications. The use of stent in anastomosis of the ureter significantly decreases operation complication rates. A urological complication that is confirmed by careful evaluation and that can be surgically corrected should be aggressively treated by experienced surgeons to avoid any graft or patient losses.

Authorship

AD: designed research, performed research/study prepared manuscript; AT and ST: performed research/study, collected data, prepared manuscript; HK, analyzed data, collected data; AG and OE: performed research/study; MT and AD: designed research.

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