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Deceased Donor Kidney Transplantation from Donors with Acute Renal Failure due to Rhabdomyolysis

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With the current shortage of solid organs for transplant, the transplant community continues to look for ways to increase the number of organ donors, including extending the criteria for donation. In rhabdomyolysis, the byproducts of skeletal muscle breakdown leak into the circulation resulting in acute renal failure in up to 30% of patients. In nonbrain dead patients, this condition is reversible and most patients recover full renal function. Seven potential donors had rhabdomyolysis with acute renal failure as evidenced by the presence of urine hemoglobin, plasma creatinine kinase levels of greater than five times the normal and elevated creatinine. One donor required dialysis. At our institution, 10 kidneys were transplanted from the seven donors. Two grafts had immediate function, five grafts experienced slow graft function and three grafts had delayed graft function requiring hemodialysis. At a mean of 8.7 months posttransplant (2.4–25.2 months), all patients have good graft function, are off dialysis and have a mean creatinine of 1.3 (0.7–1.8). In conclusion, our experience suggests that rhabdomyolysis with acute renal failure should not be a contraindication for donation, although recipients may experience slow or delayed graft function.

Key words: Acute renal failure, extended criteria donors, kidney transplant, rhabdomyolysis

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Introduction

Rhabdomyolysis is a relatively common cause of acute tubular necrosis, affecting 10–15% of hospitalized patients with acute renal failure (ARF) in the United States (1). Rhabdomyolysis results from a severe trauma, specifically a crush injury that causes muscle injury and necrosis. However, there are multiple other causes, including prolonged immobilization, electrical shock and prolonged seizure activity. Severe muscle damage releases the myoglobin heme pigment, forms casts in the renal tubules, obstructing them and causing ischemic injury and acute renal failure.

The diagnostic criteria for rhabdomyolysis include elevated creatinine kinase (CK) levels in the blood, in particular the MM isoenzyme, which arises from skeletal muscle, and not the MB isoenzyme which is cardiac in origin. CK rises 2–12 h after injury, and peaks at 1–3 days (2). Most authors agree that a CK level of greater than five times normal (or >1000 U/L) is consistent with rhabdomyolysis, although levels greater than 10 000 are usually associated with ARF (2). However, the degree of CK elevation may not always predict the development of ARF (3). Serum myoglobin and urine myoglobin are far more sensitive indicators of rhabdomyolysis, but are not routinely checked for a donor evaluation. Rhabdomyolysis may also be associated with hyperkalemia, hyperphosphatemia, hypocalcemia and metabolic acidosis. Patients with rhabdomyolysis who do not proceed to donation almost always recover renal function within 10–14 days after injury. Kidney biopsies from patients with rhabdomyolysis typically show intratubular casts and acute tubular injury similar to acute tubular necrosis (ATN) (4). It is unclear how often these changes are noted, as the diagnosis of rhabdomyolysis is not made by kidney biopsy and how flushing and storing after organ donation would affect the biopsy results.

The deceased donor waiting list continues to grow in the United States and transplant centers are looking for ways to extend the donor pool. Kidneys from donors with reversible causes of ARF are being used with an increasing frequency. This is the first reported case series of kidneys transplanted from donors with ARF from rhabdomyolysis and their subsequent recovery and function in seven transplant recipients.

Materials and Methods

Our program began to accept donor kidneys with evidence of ARF in 2007. Kidneys from donors less than 55 years old with ARF (normal or near normal admission creatinine, no past medical history of chronic renal failure and terminal creatinine >2.0) were considered for transplantation. Donor kidneys were biopsied to excluded chronic damage and evidence of cortical necrosis. Donor kidneys that did not flush well at the time of procurement

or had significant petechiae were also turned down. This is a retrospective chart review from January 2007 until December 2008 of seven donors who had evidence of rhabdomyolysis and ARF at the time of donation, and the 10 recipients of the donated kidneys. In this review, rhabdomyolysis was defined as a CK level greater than five times normal (>1000 U/L) in conjunction with the presence of blood in the urine with minimum red blood cells (RBCs) (suggestive of urine myoglobin). The urine color was also noted as hazy and tea colored urine is often present from the myoglobin casts.

All patients were informed about the donors, including the ARF and likelihood of delayed graft function (DGF), and consent was obtained. Kidneys were procured in a standard, well-described fashion. Custoidal HTK (Odyssey Pharmaceuticals) was used for preservation in two donors and Viaspan (DuPont Pharmaceuticals) was used in the other five donors. Mechanical pulsatile perfusion was used in one case. Protocol biopsies are done after transplantation at time 0, 1 month, 4 month and yearly biopsies. The biopsies for these kidneys were all reviewed by our kidney transplant pathologist. All patients are given induction immunosuppression. Our program switched from Thymoglobulin (Genzyme) to Campath (Genzyme) in August 2008. Six patients received Thymoglobulin and four received Campath in this series. Three patients had positive T- and B-cell flow crossmatches (one patient also had donor specific antibodies) and received three doses of 100 mg/kg intravenous immunoglobulin perioperatively. Patients who were of low immunologic risk were tapered off prednisone by discharge, while patients who were high immunologic risk (positive crossmatch and/or donor specific antibodies) were maintained on steroids. For maintenance immunosuppression, Prograf (Astellas) and Cellcept (Roche) were used.

Results

From January 2007 until December 2008, 357 kidney transplants were preformed, 157 from living donors. There were 200 transplants from deceased donors, including 3 combined liver kidney transplants, 3 combined heart kidney transplants and 52 simultaneous kidney pancreas transplants. The terminal creatinine was greater than 2.0 in 12 donors of 16 kidneys (8% of deceased donor kidneys transplanted), suggestive of ARF. In addition, two donors had evidence of ARF on or after admission that had normalized at the time of donation. Of the 12 donors, 7 had a CK >5× normal at the time of procurement. Five donors had normal CK (3) or no CK recorded (2) at the time of procurement. Six of the seven donors (five kidney only and one combined kidney-pancreas) were open offers to our center, and were turned down by all centers ahead of us. This included one local, two regional and three national offers for sequences 40–538.

Donors

The donor characteristics are summarized in Table 1. The donors were mostly male (86%) ranging from 18 to 57 years old (mean 31). The causes of death are listed in Table 1, and all of the donors had a cause of death (seizure, MVA) and/or significant downtime (up to 90 min) that would contribute to the development of rhabdomyolysis. The peak CK ranged from 6099 to 52 048 U/L (mean 15 307). All patients have evidence of blood in the urine, with the presence of minimal hemoglobin, which is suggestive of urine myoglobin. All of the donors were making urine at the time

Table 1: The salient donor characteristics

Donor	Age (sex)	COD	Downtime	Peak CK (U/L), MB (mg/dL)	UOP at donation (mL/h)	UA blood/ RBC appearance	Cr admit	Cr peak	Cr donation	Diuretics	HD	Time from admit to donation (h)	Time from admit to peak CK (h)	Other organs (status)
1	38 (F)	Sepsis	Unknown	8534 94.6	75	Large/3 Hazy	2.5	2.5	2.2	No	No	16	0	Heart (GGF) Kidney (GGF)
2	19 (M)	Seizure	30 min	16 284 78.1	100	Moderate/1 Amber/Hazy	1.3	3.7	3.7	Lasix	No	125	101	Liver (GGF) Liver (GGF)
3	26 (M)	OD	17 min	6874 132.8	95	Large/0–2 Hazy	4.12	4.12	1.88[1]	No	Yes	40	0	Kidney (GGF)
4	29 (M)	OD	60 min	6661 77.6	350	Large/1 Clear	1.7	2.7	2.1	No	No	84	12	Liver (died)
5	31 (M)	Multiple GSWs	Unknown	6099 N/A	220	Large/3 Amber/Hazy	1.2	5.8	5.8	Lasix	No	129	120	Liver (GGF)
6	18 (M)	MVA	None	52 084 N/A	280	3+/6–10 Hazy	1.7	2.6	2.4	None	No	80	24	Heart (GGF) Liver (GGF) Kidney (GGF)
7	57 (M)	MI	90 min	10 651 11	30	4+/0–2 Slight haziness	1	5.3	5.3	Lasix, bumex mannitol	No	48	20	Liver (GGF)

OD = overdose; GSW = gunshot wound; MI = myocardial infarction; MVA = motor vehicle accident; N/A = not available; GGF = good graft function; COD = cause of death.
[1]After hemodialysis.

Table 2: The sequential results of protocol kidney biopsies starting from the donor biopsy to the 1-year biopsy if available

	Donor (#)	Time zero	Time 1 month	Time 4 months	Time 1 year
1	6% GS (1) minimal TA	Inadequate sample	Mild IFTA	Mild IFTA	Mild IFTA
2	Mild ATN (2)	ATN[1] tubular sloughing	Mild IFTA	Mild glomerulitis	Mild IFTA
3	Mild ATN (2)	Not available	Not available	Mild IFTA	Moderate IFTA
4	Not available (3)	No abnormality	Mild IFTA	Mild IFTA	Not available
5	Not available (4)	Mild ATN	Mild IFTA	Mild IFTA	Mild IFTA
6	Mild ATN (5)	Mild ATN necrotic debris in tubule	Mild IFTA	Moderate IFTA	Not available
7	Mild ATN(5)	Inadequate sample	Mild IFTA	Moderate IFTA	Not available
8	Not available (6)	Mild IFTA	Resolving tubular injury Mild IFTA	Not available	Not available
9	Mild ATN Mild IFTA Mild fibrin (7)	Inadequate sample	Mild IFTA	Not available	Not available
10	Mild ATN Mild IFTA Mild fibrin (7)	Mild ATN Mild IFTA	Resolving ATN Mild IFTA	Not available	Not available

IFTA = interstitial fibrosis and tubular atrophy; ATN = acute tubular necrosis; GS = glomerulosclerosis; TA = tubular atrophy.
[1]This patient also had a 1-week biopsy to exclude rejection, which demonstrated patchy changes, including dilated tubules with a degenerative material in the tubules and degenerative changes in the tubules consistent with resolving donor injury.

of donation, although one patient was oliguirc (30 mL/h). One patient received hemodialysis for a potassium of 7.0 upon admission, and two patients were receiving aggressive diuresis. The terminal creatinine ranged from 2.1 to 5.8 (mean of 4.0). Although it is the policy of our program to biopsy any donor kidney with ARF, some of the biopsies are unavailable for review. The majority of the donor biopsies demonstrated mild ATN, one with some fibrin deposition, consistent with tubular damage from rhabdomyolysis (Table 2).

Recipients

The recipient outcomes are summarized in Table 3. Ten patients received kidney transplants from the seven donors. The five male and five female recipients were aged 46–73 (mean 57) and had renal failure predominately resulting from diabetes mellitus (5). Nine of the 10 patients were on hemodialysis at the time of transplant, and one patient received a preemptive combined kidney pancreas transplant. Nine patients received primary transplants, one patient received a simultaneous kidney pancreas retransplant. Three patients had positive B- and T-cell flow crossmatches. Cold ischemic time ranged from 4.7 to 31 h (mean 14.6). All patients received mannitol and lasix prior to kidney reperfusion, as per our protocol. There was no specific treatment (forced diuresis or urine alkalinization) given to the recipients for the rhabdomyolysis. Two patients had excellent, immediate graft function. Five of the 10 grafts suffered from slow graft function (a drop of less than 50% of creatinine by postoperative day 5). Three patients needed hemodialysis for DGF. One patient needed only a single hemodialysis treatment and two patients remained on hemodialysis for 10–14 days.

Time zero kidney biopsies were available for 6 of the 10 recipients, representing six of the seven donors (Table 2). Four biopsies were unavailable (secondary to poor biopsy quality, processing and intraoperative error). Five of the six available biopsies demonstrated evidence of acute tubular necrosis, and two biopsies demonstrated tubular

Table 3: Each recipient's graft function after transplant

Recipient (donor)	Slow graft function	Delayed graft function/HD	Time on HD (days)	Cold ischemic time (hours)	Follow-up (months)	Creatinine 1 month	Creatinine 4 months	Clearance 4 months	Creatinine last follow-up
1 (1)	Yes	No	0	25	25.2	1.3	1.1	53	0.7
2 (2)	No	Yes	1	4.7	19.7	1.1	0.9	62	1.1
3 (2)	Yes	No	0	5.5	19.7	0.8	0.8	56	0.7
4 (3)	Yes	No	0	15.5	17.6	1.9	1.4	55	1.6
5 (4)	Yes	No	0	31.25	11.6	1.1	1.3	45	1.5
6 (5)	No	No	0	12.5	10.1	1.2	0.9	44	0.7
7 (5)	Yes	No	0	10	10.1	0.9	0.7	62	0.7
8 (6)	No	No	0	7	6.6	0.5	1.1	N/A	N/A
9 (7)	No	Yes	10	13	2.4	1.9	N/A	N/A	1.5
10 (7)	No	Yes	14	13	2.4	2.2	N/A	N/A	1.5

N/A = not available.

sloughing and debris, consistent with rhabdomyolysis. This is further followed by a 1-week biopsy in one patient which shows progression of this process, including patchy tubular degeneration with debris in the tubules. Nine of 10 biopsies were available at 1 month, and these changes have resolved in all of the biopsies, except for 2 where the injury is still present but resolving (Table 3). Four-month and 1-year biopsies are available in seven and four patients, respectively, and only show chronic changes.

Discussion

Although there are multiple case reports detailing the development of rhabdomyolysis after kidney and other organ transplantation, there is only one other case report describing the use of donors with rhabdomyolysis for kidney transplantation (6). Up to 15% of patients with ARF have evidence of rhabdomyolysis, and it may be higher in the patients who proceed to become organ donors, since many have a history of trauma and prolonged downtime. Despite ischemic damages to the renal tubule, patients with rhabdomyolysis who do not proceed to donation usually recover renal function in 10–14 days.

Until recently, patients with ARF were excluded from kidney donation. However, as the wait list for deceased donor kidney transplantation continues to grow, the transplant community continues to look for ways to increase the number of organ donors, including expanding the criteria for donation. Recently, few centers have published series of kidney transplanted from select donors with reversible ARF, with an increased rate of DGF, but equivalent long-term function (5,7,8). Analysis of the Organ Procurement and Transplant Network (OPTN) found that in 2007 there were 434 donors with a creatinine >2.5 and an age less than 50 years old. Out of a possible 868 kidneys, 407 were recovered and 289 transplanted. Although there may be multiple reasons why these kidneys were not recovered and transplanted, it suggests that the use of young donor kidneys with ARF may be underutilized.

This series looks at a subset of donors with evidence of rhabdomyolysis at the time of donation. All seven donors had ARF, and one required dialysis. Kidney biopsies done at procurement and time zero revealed tubular injury, which resolved or was resolving at the time of their 1- and 4-month biopsies. Despite the need for hemodialysis in three recipients, all patients had normal graft function at 1 month after transplantation. Pisarski *et al*. have published the only case report describing the use of a donor who suffered from poly trauma and had a CK of 11 463 and a serum creatinine of 4.7 necessitating continuous hemofiltration at the time of donation (6). One recipient had DGF, and the other had immediate function. Kidney biopsies at 10 days were unremarkable. Kumar et al reported 55 recipients who received kidneys from donors with ARF with a 3-year graft survival of 90% comparable to recipients who received standard criteria donor kidneys without ARF. These authors reported that in 10 of the 38 donors, ARF was due to crush injury with myoglobinuric ARF. However, CK levels or other diagnostic criteria were not mentioned (6).

There have been multiple studies and recommendations published on the treatment of rhabdomyolysis, although there is no clear evidence that any therapy changes the natural course of the disease. Management for the donor should include aggressive volume replacement with a goal urine output of 200–300 mL/h, which is essential to prevent further cast formation from the myoglobin. This may be difficult in donor management, where third spacing of excess fluid may negatively affect the other organs, especially the heart and lungs. Diuresis with mannitol and lasix has been recommended, as well as the addition of sodium bicarbonate to the maintenance fluid with a goal of alkalinizing the urine to a pH of 6.5. There is no clear evidence that this is beneficial, and normovolemia must be achieved prior to diuresis.

It is not clear if recipients who receive kidneys from donors with rhabdomyolysis should be treated differently. Most kidney transplant protocols include inducing diuresis at the time of reperfusion using lasix and/or mannitol. Aggressive fluid resuscitation posttransplant may be detrimental in this patient population with the risk of pulmonary edema and congestive heart failure, unless the graft has good immediate diuresis. Since there is no longer ongoing myonecrosis in the recipient, the kidneys will recover function over time, but the patient needs to be aware of the high likelihood of DGF.

Conclusion

Rhabdomyolysis with ARF should not be a contraindication for donation, although recipients may experience slow or delayed graft function. Within 1 month after transplantation, the kidneys recovered and had normal graft function, which is confirmed by the kidney biopsy. This is in agreement with several studies that demonstrate with good donor selection that the use of kidneys from donors with acute reversible renal failure may continue to expand the donor pool.

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