CASE REPORT

Kidney transplantation in an adult patient with VACTERL association

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SUMMARY

The vertebral, anal, cardiac, tracheoesophageal, renal, and limb birth defects (VACTERL) association is a rare, non-random constellation of congenital abnormalities among which urinary tract anomalies can be included. In the presence of these anomalies, patients are suspected to have a higher rate of renal failure than average. We report a case of a 22-year-old woman with VACTERL association and consequent end stage renal failure. A live-related kidney transplant was carried out successfully and the postoperative course was uncomplicated. The patient had immediate graft function. Risk factors that may complicate kidney transplant surgery in this patient population as well as considerations relevant to peritransplant management are discussed.

BACKGROUND

VACTERL association is a non-random constellation of congenital abnormalities.¹ Originally described as the VATER association, this syndrome includes vertebral abnormalities (V), anal atresia (A), trachea-oesophageal fistula/atresia (TE) and radial/renal defects (R).¹ This was later expanded to VACTERL to include cardiac (C) malformations, more generalised limb abnormalities (L) in lieu of radial alone.^{2–4} The definition of this disorder is extensively debated, but the diagnosis is typically defined as the presence of abnormalities in three or more categories.^{3–4} It is diagnosed in 1:10 000–1:40 000 live-births, depending on the definition used.^{3–5} Its aetiology is also the subject of deliberation and a single unifying cause has not yet been established.^{3–5}

Urinary tract abnormalities are seen in approximately 60–90% of patients with VACTERL association.⁶ These abnormalities include renal agenesis, vesicoureteral reflux (VUR) and neurogenic bladder.⁶ These problems can cause end stage renal failure (ESRF) and may require kidney transplant.⁶ However, the rarity of the disorder makes it impossible to carry out large trials regarding ESRF and kidney transplant in this patient group.

Current information regarding kidney transplantation in paediatric patients with VACTERL association is based on a few small case series.^{7–10} On the other hand, published experience regarding kidney transplant in adult patients is even more scarce.⁶ We report a case of a woman with VACTERL association who underwent kidney transplant.

CASE PRESENTATION

A 22-year-old woman was admitted for live donor kidney transplantation. Her medical history was

remarkable for congenital abnormalities related to VACTERL association such as anal and vaginal atresia, tracheo-oesophageal fistula (TEF) with oesophageal atresia, hypoplastic vertebrae, spina bifida, sacral dysgenesis and right-sided club foot. During childhood, she underwent reconstructive surgeries for anal and vaginal atresia and the TEF with oesophageal atresia. During adolescence, she was diagnosed with neurogenic bladder associated with right-sided VUR. Subsequently, she was put on clean intermittent catheterisation (CIC). Since it was difficult to identify the urethral meatus, a continent urinary diversion (Mitrofanoff appendicovesicostomy) was performed 6 years prior for easy self-catheterisation. However, the patient performed CIC on an irregular basis and continued to occasionally void per urethra.

She was afflicted by recurrent pyelonephritis (at least six episodes per year, over 6 years) which required multiple hospital admissions. She developed ESRF due to neurogenic bladder, VUR and recurrent pyelonephritis, and was put on haemodialysis through a tunnelled central venous dialysis line 6 months before the kidney transplant. She continued to perform CIC and her urine amount was approximately 1 L per day. There was a history of sulfamethoxazole/trimethoprim allergy that resulted in generalised oedema and rash.

Physical examination was remarkable for a right-sided tunnelled subclavian haemodialysis catheter and an umbilical stoma in addition to several abdominal and pelvic surgical scars, in keeping with the patient's extensive past surgical history. Perineal examination revealed a single external orifice anteriorly. The associated canal seemed to lead from the urinary bladder. There was no vagina.

INVESTIGATIONS

Preoperative management included extensive urological investigations in addition to the routine pre-transplant work up.

Review of the previous urine cultures revealed recurrent urinary tract infection (UTI) episodes with multidrug resistant bacteria: *Serratia marcescens* and extended spectrum β lactamase-positive *Escherichia coli*. Antibigrams posed sensitivity to sulfamethoxazole-trimethoprim and imipenem.

Urological investigations included urinary tract ultrasonography, voiding cystourethrogram, flexible cystourethroscopy and urodynamic pressure-flow study. Ultrasonography showed bilateral marked hydronephrosis with severe parenchymal atrophy worse on the right side (figure 1). The urinary bladder wall looked mildly thickened. Voiding

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Figure 1 Preoperative ultrasound image demonstrating marked hydronephrosis and severe parenchymal atrophy of the right native kidney.

cystourethrogram revealed marked right-sided VUR in addition to incomplete bladder emptying per urethra. Flexible cystourethroscopy demonstrated a short urethra with a relatively small bladder. Urinary bladder capacity was measured as 273 mL during the urodynamic pressure-flow study. Voiding pressures were in the normal range, however, the patient required bladder emptying through the Mitrofanoff appendicovesicostomy.

Immunological investigations detected a cumulative panel reactive antibody level of 16%, which implied unremarkable sensitisation. The patient had two of six human leucocyte antigen mismatches with her donor.

DIFFERENTIAL DIAGNOSIS

- ▶ Obstructive uropathy
- ▶ Recurrent pyelonephritis
- ▶ Reflux nephropathy
- ▶ Neurogenic bladder

TREATMENT

Standard immunosuppression induction with basiliximab (20 mg, intravenous) and methylprednisolone (500 mg, intravenous) was given due to unremarkable immunological sensitisation. As a consequence of the history of sulfamethoxazole-trimethoprim allergy and recurrent UTIs with multidrug resistant bacteria, UTI prophylaxis with imipenem was started perioperatively.

Urethral catheterisation was performed under the guidance of flexible cystoscopy in the operating room. An 18 F 3-way Foley catheter was inserted. The left kidney of the donor was transplanted into the right iliac fossa. The renal graft had a single vein and artery that were anastomosed to the external iliac vein and artery, respectively. Total anastomosis time was 23 min. After reperfusion, the urinary bladder was filled with gentamicin-normal saline solution (120 mg/250 mL) through the Foley catheter. The bladder wall was thick and scarred. Although it was technically challenging, we were able to perform a non-refluxing ureteral implantation on the right anterolateral wall by Lich-Gregoir ureteroneocystostomy technique. A 6 F, 14 cm double-J stent (DJS) was inserted during ureteral implantation. A 10 F Jackson-Pratt (JP) drain was placed. There were no intraoperative complications.

Tacrolimus, mycophenolate mofetil and prednisone were given for maintenance immunosuppression therapy. The patient had immediate graft function. The Foley catheter was retained for a longer period after taking the risk factors for urine leakage (ie, technically challenging ureteral implantation, neurogenic

bladder) into consideration. It was removed on postoperative day 7 and the patient was managed by CIC, six times a day, on a regular basis, through the Mitrofanoff appendicovesicostomy. The JP drain was removed on postoperative day 8, when the output was lower than 50 cc per day.

On postoperative day 9, a sulfamethoxazole-trimethoprim desensitisation process was carried out without any complications, and subsequently the patient was transitioned from imipenem to sulfamethoxazole-trimethoprim (400 mg/80 mg) for long-term UTI prophylaxis. She was discharged on postoperative day 10 with a serum creatinine level of 72 $\mu\text{mol/L}$.

OUTCOME AND FOLLOW-UP

The patient was closely followed up in the outpatient clinic. The tunnelled haemodialysis line was removed 3 weeks after kidney transplantation. The DJS was removed 6 weeks after kidney transplantation by flexible cystoscopy per Mitrofanoff appendicovesicostomy. During the first follow-up year, the patient had four mild to moderate UTI episodes that did not require hospital admissions. Urine cultures taken during the mild UTI episodes were negative.

On the other hand, urine culture taken during the moderate UTI episode (4 months after kidney transplant) revealed *Enterobacter cloacae* resistant to sulfamethoxazole/trimethoprim but sensitive to ciprofloxacin. Urinary tract ultrasonography performed at that time excluded graft hydronephrosis and revealed reduced hydronephrosis in the right native kidney (figure 2). Oral ciprofloxacin (250 mg, twice daily) was given for 7 days. There was no later recurrence. The patient continued to have good graft function (Cr: 110 $\mu\text{mol/L}$) at 12-month follow-up.

DISCUSSION

Urinary tract abnormalities occur at a high frequency in the setting of VACTERL association.⁶ However, there are only a few reports on the clinical courses of these abnormalities and management of kidney transplantation in this patient population.^{6–10}

Koo *et al*⁷ investigated kidney transplant in 18 children with lower urinary tract dysfunction. Lower urinary tract dysfunction was affiliated with VACTERL association in one patient. Pretransplant management in these cases included renal ultrasound, voiding cystometrogram and urodynamic studies. In their approach, augmentation cystoplasty was necessitated by inadequate urinary bladder capacity or high intravesical pressures. Their surgical technique included Lich-Gregoir extravesical ureteroneocystostomy in all the patients. They recommended close follow-up and antibiotic prophylaxis for patients

Figure 2 Ultrasound performed postoperatively revealed reduced hydronephrosis in the right native kidney.

with vesicoureteral reflux and highlighted the importance of compliance with CIC post-transplant. Our approach was in line with these recommendations. Antibiotic prophylaxis and compliance with CIC significantly decreased the frequency and severity of our patient's UTI episodes.

Adams *et al*⁸ also reported their experience with paediatric kidney transplantation in patients with dysfunctional lower urinary tracts. Among a total of 66 children, two had VACTERL association. They stated that kidney transplant surgeries were technically challenging in all the cases. However, when they compared the graft survival rates, they did not find a significant difference between their study population and the general patient population (83.3% and 88%, respectively). The 1-year and 5-year graft survival rates in children with VACTERL association were 85.7% and 71.4%, respectively. UTI was the most frequent complication encountered during the post-transplant follow-up period. They claimed that recurrent symptomatic UTIs might trigger rejection episodes and cause chronic allograft nephropathy. They highlighted the importance of antireflux ureteral implantation and UTI chemoprophylaxis for prevention of UTIs. They also recommended drainage of the transplant ureter to a non-augmented urinary bladder for the same purpose.

Our experience is consistent with these recommendations. Although the transplant surgery per se was technically challenging, we were able to perform an antireflux ureteral implantation. We did not perform an augmentation cystoplasty since the urinary bladder capacity was adequate and the intravesical pressures were in the normal range. Despite being on UTI chemoprophylaxis, our patient experienced UTIs after the transplant. However, only one of those episodes was symptomatic. She did not have any rejection episodes and maintained good graft function during 1-year follow-up.

Ahn *et al*⁹ reviewed the kidney transplant outcomes in children with VACTERL association. They had seven patients with VACTERL association who underwent kidney transplantation. In contrast to Adams *et al*,⁸ these authors reported poorer post-transplant outcomes in patients with VACTERL association.⁹ However, six of their seven patients (85.7%) had a history of extensive urological surgical interventions that included augmentation cystoplasty procedures.⁹ Our patient had a Mitrofanoff appendicovesicostomy for easy self-catheterisation long before her transplant. Her pretransplant urological evaluation did not reveal findings to potentially mandate any surgical interventions.

Telkes *et al*⁶ reported the first two adult patients with VACTERL association who underwent kidney transplant. The first patient received a kidney transplant at the age of 22 years, using a cutaneous ureterostomy. During the post-transplant course, she had an acute rejection episode accompanied by a severe UTI that led to graft loss. Augmentation cystoplasty was performed subsequently and this patient received a second renal graft at the age of 24 years. However, she again experienced rejection and multiple hospitalisations due to lower UTI

episodes and distal ureteral strictures. The second patient received a kidney transplant at the age of 26 years. His post-operative course was complicated by an acute rejection episode.

Their findings, altogether, justify the recommendations of Adams *et al*,⁸ who stated that peritransplant urological reconstructive surgeries might be problematic, and UTI episodes might trigger rejection episodes and eventually cause graft loss.

Learning points

- ▶ The vertebral, anal, cardiac, tracheoesophageal, renal, and limb birth defects (VACTERL) association can include urinary tract abnormalities such as neurogenic bladder and vesicoureteral reflux, which can cause end stage renal failure and may require kidney transplantation during adulthood.
- ▶ Post-transplant recurrent urinary tract infection is a frequent complication encountered in adult patients as well as in children.
- ▶ Comprehensive pretransplant urological evaluation, antireflux ureteral implantation, antibiotic prophylaxis and close follow-up are crucial for prevention of post-transplant recurrent urinary tract infections and consequent graft loss.

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Competing interests None declared.

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