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Clinical Transplantation

Case Report

Transfer of ureteral carcinoma in a transplanted kidney presenting by early stenosis of the proximal ureter

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Abstract: A 71-yr-old male kidney transplant recipient suffered from delayed graft function. Eighty days after transplantation complete obstruction of the proximal ureter was observed, complicated by recurrent urinary tract infections. Two months later, the donor kidney was removed because of infectious complications and inadequate arterial perfusion. Histological examination of the removed graft showed signs of rejection as well as a low-grade papillary urothelial cell carcinoma of donor origin in the ureter. The remaining donor ureter was removed subsequently and showed no further signs of malignancy. Follow-up of the patient until 12 months after surgery did not reveal recurrence of the tumor. This case report is the first to describe accidental transfer of urothelial cell carcinoma in the ureter by transplantation, highlighting the possibility of malignancy when early stenosis is not related to the anastomosis. It again emphasizes the need for precise and cautious screening of organ donors, especially those of higher age.

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Key words: carcinoma – delayed graft function – donor malignancy – donor-to-host transmission – kidney transplantation – ureteral stenosis

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Accidental transfer of malignancy from donor to recipient is one of the most fearsome complications in transplantation. It has been described for numerous types of malignancy and in most types of transplantation. Its reported incidence as part of the total number of transplantations is 0.2% (1). For kidney transplantation, the recommendations to minimize its occurrence have been postulated before (2). These recommendations are still appropriate, consisting of stringent evaluation of the donor's medical history and cause of death, including signs of metastases that may point to a primary tumor in the donor organ. Accordingly, careful examination of donor organs should be performed, including the use of ultrasound and frozen section histology. However, even when all criteria of careful evaluation are met, the possibility of cancer transfer in transplantation still exists. Its presentation varies greatly, complicating timely discovery and subsequent adequate treatment.

In this case, urothelial cell carcinoma (also referred to as transitional cell carcinoma) of the ureter was transferred from a deceased donor into a kidney transplant recipient. Its presentation was extraordinary, by stenosis of the proximal ureter shortly after transplantation. To our knowledge, this type of transfer and presentation have not been reported before. This report discusses the features of and desired treatment for post-transplantation ureteral stenosis as well as urothelial cell carcinoma.

Case report

A 71-yr-old male received a kidney transplant from a deceased donor of about the same age as part of the Dutch "old-for-old" kidney transplantation

program. The recipients' medical history was extensive and included appendectomy, inguinal hernia, hypertension, deep venous thrombosis and hypertensive nephropathy. He had been on hemodialysis for four yr and had no remaining urine production. The transplanted kidney was recovered from a 70-yr-old male donor deceased from subarachnoidal hemorrhage after trauma. The donor's medical history included a cholecystectomy and over 20 cigarette pack years. The kidney was 2-2-2 HLA mismatched. No abnormalities were found upon macroscopic inspection of the graft. It was transplanted into the right iliac fossa, re-establishing the urinary tract through ureterocystostomy by Lich–Gregoir. Cold and warm ischemia times were 20 h and 35 min, respectively. Immunosuppression consisted of cyclosporine (Neoral, Novartis, Arnhem, The Netherlands), prednisolone, and mycophenolate mofetil (Cellcept, Roche, Mijdrecht, The Netherlands). Kidney function improved slowly in the first week after transplantation. After one wk, creatinine levels did not further decrease spontaneously (Fig. 1). The patient experienced high cyclosporine serum levels and needed intermittent hemodialysis. Methylprednisolone was administered to treat suspected acute rejection, which could not be confirmed by biopsy.

A rise in creatinine levels was reason to perform ultrasonography on day 36 after transplantation, showing mild hydronephrosis. Placement of a nephrostomy catheter at that time did not improve kidney function. Secondary rejection therapy using ATG Merieux (Genzyme, Naarden, The Netherlands) was given and maintenance immune suppression was changed from cyclosporine to tacrolimus (Prograft, Astellas, Leiderdorp, The Netherlands). Replacement of the leaking nephrostomy was followed by a decrease in creatinine levels (Fig. 1). Eighty d after transplantation, pyelography revealed a complete obstruction of the proximal ureter

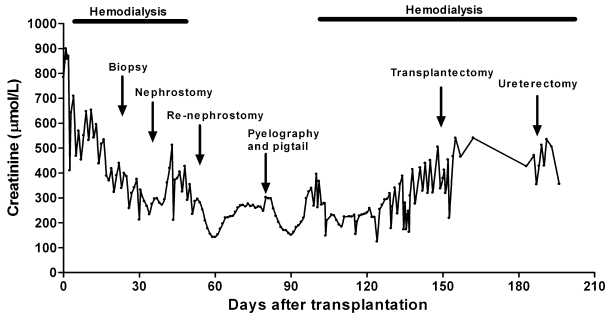

Fig. 1. Overview of the patient's serum creatinine levels (µmol/L) after transplantation. Arrows indicate relevant interventions.

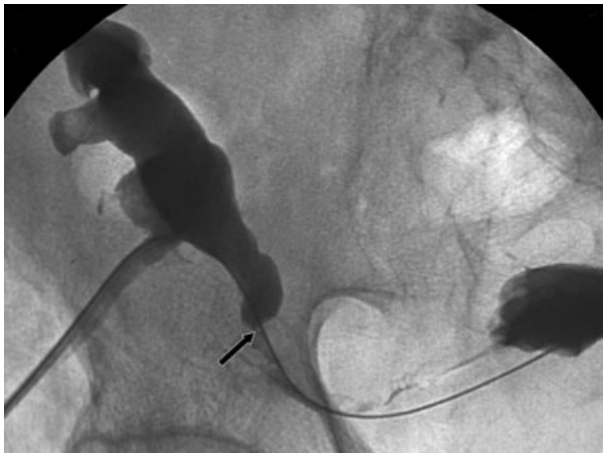

Fig. 2. Pyelography 11 wk after kidney transplantation. Total obstruction of the proximal ureter (arrow) can be observed after contrast administration through the nephrostomy catheter on the left. Note the guide wire used for placement of the double pigtail catheter running from the renal pelvis to the bladder.

(Fig. 2). A double pigtail catheter was placed along the ureter into the bladder.

During the whole post-transplant period, the patient suffered from recurring urinary tract infections. Urine cultures yielded *Enterobacter cloacae* and *Enterococcus faecalis*, which became multiresistent after several antibiotic treatments. Later, other infectious complications occurred such as *Pneumocystis carinii* pneumonia and *Cytomegalovirus* reactivation. The patient further experienced several cardiovascular complications (diastolic heart failure, angina pectoris and atrial fibrillation), was diagnosed with type II diabetes mellitus, and again needed intermittent hemodialysis.

Five months after transplantation the donor kidney was removed because of the combination of a non-functioning graft, infectious complications and insufficient arterial graft perfusion as demonstrated by renal Tc-99m MAG3 dynamic scintigraphy.

Histological analysis of the removed graft showed signs of vascular and interstitial rejection. Unexpectedly, low-grade non-invasive papillary urothelial carcinoma was observed in the donor ureter (Fig. 3). Upon this finding, additional surgery was performed, removing the remaining part of the donor ureter and the ureterocystic anastomosis. No additional signs of malignancy were found and during 12 months of follow-up, no new signs of cancer were observed. The DNA profiles of donor kidney tissue and tumor were compared using a PCR-based Short Tandem Repeat analysis kit (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands), confirming that the tumor was of donor origin.

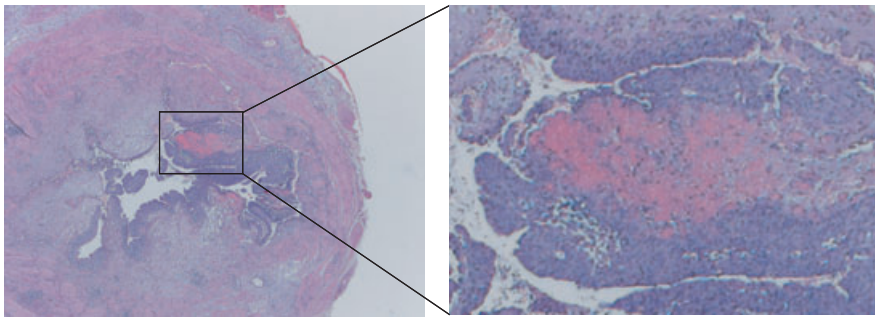

Fig. 3. (A) Cross-section of the ureter excised during transplantectomy, showing multilayering and crowding of mildly atypical cells, as seen in low-grade non-invasive papillary urothelial carcinoma (hematoxylin–eosin, 20×). (B) The lesion in more detail (hematoxylin–eosin, 100×).

Discussion

Ureteral stenosis is a rather common complication after kidney transplantation, with incidences ranging from 0.9% to 25% (3, 4). Two types can be distinguished: early and late stenosis. Early stenosis is most often due to complications regarding the ureterovesical anastomosis. Introduction of pigtail ureterovesical stents in the first period after transplantation has greatly reduced its incidence (3). Early stenosis of the proximal part of the ureter, as seen in our case, often is a result of ischemic complications. Late stenosis can have many different etiologies, among which malignancy developing during a long period of immunosuppressive treatment.

Post-transplant development of carcinoma related to the renal graft is not uncommon: the percentage of renal carcinomas compared to the total amount of *de novo* malignancies rises from 3% to 4.5% (2). To our knowledge, transferred malignancy as a cause for early stenosis after kidney transplantation has not been described before. In this case the first signs of obstruction caused by the carcinoma were found within the transplanted tissue three wk after transplantation, implying its donor origin. When in doubt about the origin of the tumor fluorescent *in situ* hybridization, HLA- or DNA typing (as performed in this case) may be of additional value (5, 6). Interestingly, the other kidney from this donor that was also transplanted still shows good graft function.

The upper tract urothelial (transitional) cell carcinoma found in this patient is a relatively rare type of malignancy with an incidence of around 1/100 000/yr, accounting for 5–7% of all renal tumors (7). Survival rates depend on disease staging, with five-yr survival ranges described from 100% for non-invasive superficial carcinoma to 0% for grade IV tumors (7, 8). Treatment also depends on the stage of the disease and may consist of endoscopic, laparoscopic or open resection of the tumorous tissue. The efficacy of adjuvant therapy (chemotherapy, immunotherapy) remains to be determined (6). In more advanced stages, laparoscopic or open nephro-ureterectomy is warranted.

The occurrence of urothelial cell carcinoma after kidney transplantation has been described before (5, 9, 10). However, in all these cases it developed years after transplantation. Patients diagnosed with malignancy after transplantation, be it transferred or newly diagnosed, should be treated with adequate reduction or withdrawal of immune suppression, as well as appropriate regular treatment of the malignancy. In our case, nephro-ureterectomy had already been performed due to non-function of the graft. Removal of the remaining ureter was needed in view of the diagnosis of carcinoma.

In conclusion, this case report is the first to describe transfer of urothelial cell carcinoma by transplantation. Despite the low reported incidence of this kind of complication, early stenosis of the ureter, not related to the anastomosis should be considered suspect for malignancy. Swift and adequate treatment of this iatrogenic complication is warranted to minimize unfavorable consequences for the patient.

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