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Post Renal Transplant *De Novo* Urothelial Carcinoma in Graft Kidneys: A Mini Review

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Abstract

Urothelial Carcinoma is any of several types of cancer arising from the tissues of the urinary bladder. Symptoms include blood in the urine, pain with urination, and low back pain. It is caused when epithelial cells that line the bladder become malignant.

Risk factors for Urothelial Carcinoma include smoking, family history, prior radiation therapy, frequent bladder infections, and exposure to certain chemicals. The most common type is transitional cell carcinoma. Other types include squamous cell carcinoma and adenocarcinoma. Diagnosis is typically by cystoscopy with tissue biopsies. Staging of the cancer is determined by transurethral resection and medical imaging.

Specifically, regarding Urothelial Carcinoma (UC), renal transplant recipients have shown a 3-fold increase in rates of *de novo* urothelial carcinoma, compared to non-transplant patients. Most of these cases have occurred in the bladder (76%-100%), followed by native kidneys and ureters (8%-24%), with rare cases occurring in the graft kidney (0%-4%). Furthermore, in these rare cases of *de novo* donor derived post renal transplant UC, studies have shown a high percentage of these tumors presenting as high grade and at least T2 stage. Rare studies have classified tumors that have occurred or included organs downstream of the graft kidney as donor derived using molecular techniques which include karyotype analysis (XY chromosome studies) and short tandem repeat studies. Donor derived UC remains an important tumor to further characterize, as existing literature suggests that they may have an increased tendency to present at higher grade and stage than another post-transplant UC. We aim to provide a brief review of the literature.

Keywords: Urothelial carcinoma; Kidney transplant; Therapy

Abbreviations

UC: Urothelial Carcinoma.

Introduction

Kidney transplant or renal transplant is the organ transplant of a kidney into a patient with End-Stage Kidney Disease (ESRD). Kidney transplant is typically classified as deceased-donor (formerly known as cadaveric) or living-donor transplantation depending on the source of the donor organ. Living-donor kidney transplants are further characterized as genetically related (living-related) or non-related (living-unrelated) transplants, depending on whether a biological relationship exists between the donor and recipient.

Kidney transplantation has been established as the treatment of choice for patients with end-stage renal disease. With advances in immunosuppressive regimens, transplant patients have a better quality of life and a significant survival benefit compared to those continuing dialysis. However, transplant patients have a higher risk of developing secondary malignancies post transplantation, owing to their extended life expectancy and chronic immunosuppressive status. Malignancy after transplantation has become the third leading cause of death in renal transplant recipients. Compared to the general population, post-transplant patients have a 7-fold increased risk of developing Renal Cell Carcinoma (RCC) in the native kidney, where it portends a significantly worse prognosis than similar tumors arising outside of the transplantation setting. Risk factors include end-stage renal disease, longer time on dialysis, and older ages at transplant. Kidney transplant recipients also have an increased risk of developing Urothelial Carcinoma (UC) in the bladder and the upper genitourinary tract, which is associated with infection with the BK polyomavirus. However, donor-derived UC is rarely reported. We herein report on a high grade papillary urothelial carcinoma arising in a donor renal allograft.

Solid organ transplant has been a gold standard of treatment for patients with end stage kidney disease, and long term follow up of these patients has shown cancer to be an important determinant of mortality. Malignancy is the third leading cause of mortality in transplant recipients and a growing body of literature has highlighted *de novo* malignancy as an important long-term outcome to consider in these patients. In renal transplant recipients, the overall incidence of *de novo* malignancy ranges from 6% to 11%, which is 4 to 5 times higher than renal malignancy in the general population [1,2]. Furthermore, recent studies have shown that the incidence of *de novo* malignancy in renal transplant recipients is the highest among solid organ transplant recipients in certain populations. Specifically, with regard to Urothelial Carcinoma (UC), renal transplant recipients have shown a 3-fold increase in rates of *de novo* urothelial carcinoma, compared to non-transplant patients [2]. Furthermore, these urothelial carcinomas can present as *de novo* malignancies in native kidneys and bladder, and donor derived lesions in the upper urinary tract of graft kidneys, or native bladder, suggesting a tendency for drop metastasis, and complicating the patient's post-transplant long term outcome [1,3,4]. Given the increasing attention drawn to *de novo*, donor derived urothelial carcinoma post renal transplant, we aim to provide a brief review of the literature.

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Literature Review

Epidemiology

The incidence of *de novo*, post-transplant urothelial carcinoma ranges from 0.2% to 4.1% [5-7]. The majority of these cases have occurred in the bladder (76%-100%) followed by native kidneys and ureters (8%-24%), with rare cases occurring in the graft kidney (0%-4%) [5,6,8]. Often the urothelial carcinoma will be present in both the bladder and either one or both upper urinary tracts, with some studies citing almost 30% of cases of *de novo* urothelial carcinoma occurring at multiple sites. While cases that develop in the graft kidney are likely to be donor-derived, cases occurring in the bladder have also been shown to be derived from donor cells using molecular studies. Furthermore, although *de novo*, post-transplant renal cell carcinoma has a higher incidence in western populations, urothelial carcinoma is the most common *de novo* urogenital malignancy in renal transplant patients in Asian countries, specifically, among patients of Taiwanese descent [8].

Etiology

Post-transplant malignancies, including *de novo* post-renal transplant urothelial carcinomas, are thought to be caused by complex interactions of genetic and environmental factors, immune status, and infection with BK Virus. Rare studies including molecular analysis of *de novo* urothelial carcinomas have reported concordant findings of these tumors being MSI stable, but showing a range of molecular alterations, including TERT amplification, loss of *CDKN2A/CDKN2B, EGFR* and *RAF1* amplification, and frame shift mutations at *KDM6A* (L945fs∗25) [3,4]. Moreover, cyclophosphamide, analgesic abuse, and certain herbal medications have been shown to be associated with *de novo* post-transplant urothelial carcinoma. Specifically, phenacetin (banned in 1981), and mixtures of analgesics used in excess can cause analgesic nephropathy, and subsequent urothelial carcinoma, while Chinese herbal medicines containing aristolochic acid have also been associated with development of post-transplant urothelial carcinoma [5-7].

Although older studies have cited immunosuppressive therapies as causes for post-transplant malignancies, newer studies have shown no significant differences in *de novo* UC incidence with regard to combination or duration of immunosuppressive therapy. Studies examining the effect of mycophenolate use showed mixed results, with some showing it to be an independent risk factor in patients without diabetes or hypertension, while in other studies, mycophenolate is not associated with a difference in UC incidence. However, immunosuppression is associated with BK virus reactivation and BK virus nephropathy and subsequent UC post-transplant [5-10].

Discussion

Use of deceased donor kidneys, and older age at the time of transplantation have been associated with increased incidence of *de novo* post-transplant UC. These studies have shown the median age at transplantation to fall between 50 and 60 years, while median age at UC diagnosis falls between 60 and 70 years. Median times from transplantation to UC diagnosis range from 48 months to 66 months [6,7]. In addition, large studies involving predominantly Asian populations have shown female sex to be significantly associated with development of UC, while no such results have been shown in studies with predominantly western populations [5,8]. The initial presenting symptom of UC in these patients is macro or microscopic hematuria, or abnormal urine cytology findings, highlighting the importance of comprehensive follow up.

The vast majority of *de novo* post renal transplant UC occurs in the native organs, either the bladder or native kidneys and ureter, with rare case reports showing donor derived tumors arising in the graft kidney. Large-scale studies examining western populations show the majority of tumors (68%-100%) are confined to mucosa or submucosa (Ta-T1) and demonstrate a normalized ratio of low grade to high grade morphology (G1/G3) shifted toward high grade (G3). On the other hand, similar studies in Asian countries have shown the majority of tumors being higher stage (at least T2) [5-10]. Also, specifically in *de novo* donor derived post renal transplant UC, studies have shown a high percentage of these tumors presenting as high grade and at least T2 stage. Rare studies have classified tumors that have occurred or included organs downstream of the graft kidney as donor derived using molecular techniques which include karyotype analysis (XY chromosome studies) and short tandem repeat studies [3,11]. A summary of findings in donor derived UC is provided in Table 1 [3,4,11-22].

Reference No	Age at transplant	Gender/ KT Type	Immuno suppressant	Initial presentation	Age at UC diagnosis	UC Grade	UC Stage	Interval KT to UC (month)	Treatment	F/U (Months)
[20]	30	M/LRDKT	Steroid, FK, MMF	Malaise, nausea, ureteral obstruction	62	High	T3NXMX	384	NUx	Dead (0)
[22]	68	M/DDKT	Steroid, FK, MMF	Gross hematuria	78	High	T3NXMX	120	NUx, Partial Cystectomy	Alive (13)
[4]	51	F/DDKT	Steroid, FK, MMF	Lower abdominal pain	60	High	T4N2M0	108	Radical NUx, ICI	Alive (34)
[18]	28	F/LRDKT	N/A	Gross hematuria	44	High	T3NXMX	192	NUx, Cystectomy	Alive (12)
[21]	61	M/DDKT	N/A	Gross hematuria	69	High	T4N3M1	96	Radical NUx, ICI, Radiation therapy	Alive (12)
[19]	41	F/DDKT	Steroid, CsA, AZA, MMF	No symptom	53	High	T3NxMx	147	NUx	Alive (94)
[17]	49	F/DDKT	Steroid, FK, MMF	Fever, Flank Pain, urinary symptoms	61	High	T3NxMx	144	NUx	Alive (24)
[17]	57	F/DDKT	Steroid, FK, MMF	No symptom	59	High	T3NxMx	14	NUx	Alive (12)
[16]	46	M/DDKT	Steroid, CsA, AZA	No symptom	52	Low	T2NxMX	72	Partial Nephrectomy	Alive (14)
[15]	58	M/DDKT	Steroid, FK, MMF	Gross hematuria	67	High	T2N3M1	108	CRTx	Dead (1.9)
[14]	29	M/LDKT	Steroid, CSA, MMF	Gross hematuria	40	Low	T2NxMx	132	NUx+CRTx	Alive (24)
[13]	23	M/DDKT	N/A	Asymptomatic microscopic hematuria	30	High	T3NxMx	84	NUx	N/A

[12]	57	M/LDKT	FK Sirolimus	No symptom,	69	High	T3NxMx	144	NUx	Alive (12)
[3]	28	F/LDKT	Steroid, AZA	UTI	62	High	T1N1M1	408	NUx	Alive (44)

Abbreviations: AZA: Azathioprine; CRTx: Chemoradiotherapy; CsA: Cyclosporine A; DDKT: Deceased-Donor Kidney Transplantation; F: Female; F/U: Follow-up; FK: Tacrolimus; ICI: Immune Checkpoint Inhibitor; KT: Kidney Transplantation; LDKT: Living Donor Kidney Transplantation; M: Male; MMF: Mycophenolate Mofetil; N/A: Not Available; NUx: Nephroureterectomy; UC: Urothelial Carcinoma; UTI: Urinary Tract Infection.

Table 1: Clinicopathological characteristics of urothelial carcinoma in graft kidney.

Conclusion

De novo, post-transplant UC is becoming an increasingly apparent long-term risk in patients undergoing renal transplant, associated with differences in ethnicity, age at transplant, type of transplant, and unclear mechanisms related to immunosuppression and viral infection. Furthermore, donor derived UC, as a subset of these tumors, remains an important tumor to further characterize; existing literature suggests that they may have an increased tendency to present at higher grade and stage. In particular, molecular studies have shown promise in helping to establish *de novo* post renal transplant UC as being donor derived, while also contributing to identification of molecular patterns in these tumors.

Acknowledgment

N/A

Conflicts of Interest

The authors have no conflicts of interest to report.

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