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Genitourinary Neoplasia after Kidney Transplantation

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Introduction

The incidence of cancers in kidney transplants has steadily increased following a dramatic rise in the number of renal transplantations, use of potent immunosuppressive drugs and longer survival for transplant recipients (1). Consequently, neoplastic disorders are an important cause of the late morbidity and mortality in renal transplant recipients (RTRs). Although tendency to develop skin cancer (2) and lymphoproliferative disorders (3) is clearly increased after renal transplantation, the association between this setting and genitourinary tumor is not clearly known. There have been a few reports on the incidence of malignancy from transplant registries. It is difficult to precisely compare the incidence with that in the general population using data from small, single-center studies (1).

Renal Cell Carcinoma (RCC) in RTRs

Primary RCC accounts 4.6% of all malignancies in RTRs, 90% in native kidneys and 10% in the allograft (4-5). Only 45 cases of allograft RCC have been reported by the Cincinnati Transplant Tumor Registry (6). Apart from a few isolated case reports, there have been only three largest case series including 3 of 1250, 5 of 1073 and 8 of 2050 RTRs had RCC (4-5, 7). Between 1984 and 2008, we diagnosed five RCC among 5532 kidney transplants (1). Several risk factors have been associated with RCC in renal transplant recipients include increasing age, male gender, previous exposure to carcinogens, and genetic predisposition (1, 8-9). Other risk factors are immunosuppression agents, acquired cystic kidney disease (ACKD), older age of donor (5, 8).

Although there is no treatment consensus, partial nephrectomy and total graft removal are the first recommended options (10). Radical nephrectomy brings the recipients back to dialysis, which is associated with a significantly decreased life expectancy (5). In selected patients, Nephron-sparing surgery, a good alternative to radical nephrectomy in small tumors, seems to be a safe procedure that allows an acceptable quality of life and prevents an early dialysis (4). Radio frequency ablation and cryoablation are other alternatives to surgery (11).

The modification of the immunosuppressive regimen after detection of the cancer is still a matter of debate. In a retrospective study, a higher tumoral grade in kidney transplants on cyclosporine was seen compared to those receiving azathioprine (12). The decreased or cessation of immunosuppressive drugs should be further evaluated since its effect on tumor growth is unknown (4). On the other hand, experimental data have shown that rapamycin may inhibit tumor cell growth and prevent RCC progression (13). Since rapamycin does not increase the risk of malignancy, patients presenting with RCC in the renal graft can be switched to sirolimus (4-5)

We recommend a strict follow-up with annually ultrasonography, especially in high-risk renal transplant patients with ACKD. Prompt and early diagnosis is the obvious cornerstone for successful management of these patients. Surgical treatment at an early stage is the only curative treatment for RCC that is associated with promising outcome at early diagnosis and management (8).

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Bladder Transitional Cell Carcinoma (TCC) in RTRs

Bladder cancer in the kidney transplants is generally uncommon (14). The incidence of TCC of the bladder in RTRs has not been known, and only a few studies have evaluated its prevalence. In a series of 3130 patients at the University of Wisconsin Hospital from 1980 to 1994, the relative risk of TCC of the bladder developing among RTRs has been estimated to be 3.31 times that of the normal population (15). In addition, the United Network for Organ Sharing database reported 0.024% (31 of 129,238 RTRs) prevalence of bladder cancer and the Israel Penn International Transplant Tumor Registry contained information on 135 patients with TCC of bladder representing 0.84% of all reported malignancies (16). To evaluate this issue further, Viraj A. Master, with the University of California, San Francisco, United States and colleagues retrospectively reviewed a transplant database from their institution containing information on 6,288 RTRs performed between 1964 and 2002. The researchers identified 7 kidney transplants with bladder cancer at their institution. Invasive TCC developed in 5 patients at a median of 2.8 years after transplant. They concluded RTRs in whom TCC develops tend to present with invasive disease (16). In our series, TCC of the bladder (7 of the 5532 patients who underwent kidney transplantation) was rare but it was the most common genitourinary cancer after renal transplantation (1). Several reports from Taiwan had indicated an unusually high prevalence of TCC among kidney transplant recipients. Kao et al. (17) reported that 24 recipients developed TCC, which accounted for 43.6% of all the identified malignancies. In another study, prevalence of TCC was 4.1% among 730 RTRs, and it was the most common type (43.5%) of malignancy after kidney transplantation (18). Again, in a series of 663 recipients (19), TCC was diagnosed in 17 (2.5%), of which six involved the urinary bladder. These high prevalence rates were attributed to the longstanding analgesic nephropathy (RR= 2.6), Chinese herbs (RR= 5.2) and chronic arsenic poisoning from intake of underground water sources (RR=2.5) (17-18). The prevalence of bladder carcinoma among the Egyptian renal transplant population was 0.37% (7 of 1865 RTRs) and accounted for 9.2% among cases who developed a malignancy; this risk is relatively high. It could be explained, in part, by the high prevalence of bilharzial infestation among the Egyptian population; there was evidence of bilharzial cystitis in five of the seven cases (20).

Although traditional risk factors for TCC development are important, other risk factors likely play a role, including older age, male gender, immunosuppressive therapy, infections with oncogenic viruses (e.g., human papilloma virus), cigarette smoking (1, 15, 20). The previous period of uremia and dialysis has also been suggested as a cofactor (18, 20). Nonetheless, in an epidemiological study by Birkeland et al, the increased tumor risk happened after kidney transplantation and not during dialysis (21). The main presenting symptom in the RTRs was painless hematuria (18, 20). Despite a higher incidence of hematuria in this population, the urologic evaluation should be thoroughly investigated, with emphasis on the use of urine cytology, endoscopy and imaging, for each non-infected renal allograft recipient who presents with microscopic (or gross) hematuria to exclude malignancy. In addition, this cancer may be more aggressive than in the general population (15, 20). Early diagnosis and management are important in such patients as these tumors are. Early urologic screening and prompt management are strongly recommended in such patients, because they usually aggressive and rapidly progressive (18). However, incidence of false-negative results of urine cytology study before biopsy procedure was high (76.7%). Thus, invasive study such as cystoscopy combined with cytology is still the most widely accepted method for bladder cancer screening in all kidney recipients at high risk for TCC (18, 22).

Furthermore, it is generally believed that TCC in the transplant population is a rapid progression of invasive disease, respond poorly to chemotherapy and associated with poor outcomes. In general, management of invasive disease should consist of radical extirpative surgery, and urinary reconstructive options that maintain quality of life can be offered to these patients without increasing morbidity (14, 23). The ileal conduit was used for diversion and orthotopic bladder substitution is feasible with a good functional outcome for patients in whom cystectomy is indicated (20, 24). In addition, a cystoscopy with lavage cytology testing of the bladder should be performed twice a year (25). Adjuvant intravesical BCG immunotherapy is considered the treatment of choice in the prophylaxis of high-grade superficial bladder carcinoma and in the treatment of carcinoma in situ (CIS) of the bladder (26). Theoretically, immunosuppression is a contraindication because of the risk of severe morbidity and sepsis. However, Palou et al (27) reported an intravesical BCG therapy in superficial bladder cancer and/or CIS in three renal transplant patients can be an effective option, with no complications (27).

It is also interesting that the use of sirolimus instead of calcineurin inhibitors was followed by regression and/or cure in patients who developed Kaposi's sarcoma. However, such experience has not been reported yet among individuals with bladder cancer (20).

Prostate cancer after kidney transplantation

Although the increased rate of renal transplantation and graft survival in men aged > 50 years has resulted in a larger number of patients reaching the age group that is at risk for prostate cancer, the incidence in transplant recipients is a matter of controversy (28). The real incidence of prostate cancer in RTRs is not well defined but can vary from levels that are lower than in the general population to levels as high as 5.8% (29-30). In our experience, the incidence of prostate cancer was low (1 of all 5532 RTRs) (1). In addition, some researchers have found prostate cancer in 30% of immunosuppressed men submitted for transurethral resection of the prostate, considerably higher than the rate in non-transplanted men (31). These facts have prompted renal transplant surgeons to actively screen kidney transplant patients for prostate cancer. Routine periodic digital rectal examination, serum prostate-specific antigen screening, and prostate needle biopsy as needed in RTRs above 50 years of age are recommended for the diagnosis of prostate cancer. This could result in the detection of early stage cancers, allow definitive therapeutic intervention to help achieve midterm survival, and finally, to precisely determine the incidence of prostate cancer in these patients.

Due to the rarity of prostate cancer after renal transplantation there are no guidelines for its management. Most patients (84%) with prostate cancer being detected after solid organ transplantation are diagnosed with localized disease (32). Surgical treatment was our preferred method of treatment in renal transplant recipients with localized prostate cancer, although there is no consensus about the best treatment modality in this setting. Radical prostatectomy can be performed with perineal, retropubic, and laparoscopic approaches. The final decision is based on surgeon expertise. Radical retropubic prostatectomy in RTRs as a curative treatment is safe, effective, and can be easily performed in the same manner as described by Walsh without any additional risk and has encouraging results in patients with locally confined prostate cancer (30). The only necessary technical modification is the avoidance of ipsilateral lymphadenectomy to prevent damage to the transplanted organ (30). There is a report that Robot-assisted radical prostatectomy is feasible in the carefully selected RTRs with favorable oncologic, continence, and potency outcomes (33).

The modification of immunosuppressive regimens is another unresolved issue. Prostate cancer is a

slow-growing tumor in the majority of cases. Some authors decided not to make any modification in the immunosuppressive regimen of RTRs and to observe them (30). Although there is no evidence for immunosuppression modification, the use of sirolimus in patients with a history of malignancy instead of calcineurin inhibitors may be logical.

Uterine and Cervical Neoplasia in RTRs

Although the Pap smear is the best screening test for early identification of uterine and cervical neoplasia, it has a false-negative result of 15% to 20%, so in the high-risk population colposcopic examination of the cervix is also recommended (34). Cervical tumor, a virus-related malignancy, is more aggressive and develops rapidly in RTRs. The American College of Obstetrics and Gynaecology specifies that women of high-risk groups should be screened more frequently. The two transplantation societies recommend annual cervical cancer screening with Pap smear and pelvic examination in all adult female kidney transplants (35). An increased incidence of cancer of the cervix and the body of uterus in young patients with a functioning graft was reported by the EDTA-ERA registry (36). On the other hand, Morrison et al. reported a declining incidence of cervical and uterine neoplasia in their study of older kidney recipient patients (37). In our study, we did not find significant correlation between these cancers in RTRs compared to the control group with 2 years on average interval from surgery (34).

Anogenital malignant neoplasia may occur with a 14-fold increased incidence, and human papilloma virus (HPV) infection has been recently identified as the leading cause of cervical carcinoma (38). Some investigators recommended the use of HPV DNA as an adjunct to cytological screening in female renal transplant population. HPV DNA has been shown to perform better than cytological testing, with a test sensitivity of almost 95% (35). It is obvious that the use of immunosuppressive agents after kidney transplantation may lead to reactivation of latent diseases and may cause an increased incidence of oncogenic cervical HPV infections (HPV 16 and 18) (39-40).

Breast Cancer in kidney transplanted females

Breast cancer does not appear to increase in incidence among RTRs. However, because breast cancer is quite common, transplant patients should pay particular attention to their breasts, with self examination and attendance at breast screening clinics. The overall incidence of breast cancer was significantly low (41). There was no increase in the incidence of breast cancer in Cincinnati Transplant Tumor Registry (42). Additionally, in a large collaborative transplant study registry of Dr. Opelz, in over 100,000 patients, the cumulative incidence of tumor at 10 years was 7%; however, there was no increase in the incidence of breast cancer. In other study, relative risk of breast cancer was not also significant (43). Nevertheless, this study showed a nearly 3-fold increased rate of breast cancer within the first year in kidney transplanted females when compared with the general population; however, the incidence then decreased in second and third years (43). Although the risk may not be significantly increased, there is certainly a propensity toward more breast cancers as the total number of surviving transplant patients grows (44).

Recommendations for breast cancer screening in the renal transplant population are based on screening guidelines in the general population. Most international guidelines suggest screening to commence between 50 and 69 yr of age for all female RTRs. Screening intervals recommended by most societies are between 1 and 2 year (35).

Conclusions

Although the genitourinary tumors are uncommon occurrence after renal transplantation, early

diagnosis is essential to prompt and successful treatment among RTRs. Thus, screening tests should be periodically undergone in these patients.

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