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Original contribution

Polyomavirus large T antigen is prevalent in urothelial carcinoma post–kidney transplant☆,☆☆

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Summary Viral pathogens have been associated with both infectious disease and neoplasia in transplant recipients. Polyomavirus is emerging as a potential causative agent for genitourinary tract cancer in post–kidney transplant patients. Human papillomavirus (HPV) has a proven role in squamous cancers, but has not been studied in genitourinary malignancies in transplantation. Of 2345 kidney transplants performed at our center over the past 20 years, we identified 16 patients with 20 genitourinary cancers (0.7%), including 13 bladder/ureter carcinomas, 5 renal cell carcinomas (RCCs), and 2 prostate carcinomas. We performed immunohistochemical staining for polyomavirus large T antigen and p16, followed by in situ hybridization for HPV in p16+ cases. Four cases of high-grade invasive urothelial bladder carcinomas were positive for large T. Large T+ urothelial carcinomas developed at least 8 years posttransplant in young men, 3 with history of BK polyoma viremia, 2 of whom had native kidney failure due to reflux/obstruction. In situ hybridization for high-risk HPV was negative in all tested cases. Overall, 3 patients died of carcinoma. All 5 RCCs were negative for both large T and p16; 2 prostate cancers were p16 negative and p16+/HPV negative, respectively. Thus, our study shows a relatively high prevalence of large T antigen in urothelial carcinoma in kidney transplant patients (31%), but not in RCC. Although sample size is small, young patients with obstructive disease may be at particular risk for developing large T-positive urothelial carcinoma. Overall, our data further support the necessities of long-term cancer surveillance for renal transplant patients.

1. Introduction

Immunosuppressed transplant recipients have increased susceptibility to viral and other infections; furthermore, there is increased incidence of certain cancers in transplant populations, hypothetically associated with decreased immune surveillance. Evidence associating various viruses with human oncogenesis is accumulating, and some viral-associated cancers are especially prevalent in the transplant population, for instance,

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posttransplant lymphoproliferative disease (Epstein-Barr virus), anogenital carcinomas (human papillomavirus [HPV]), dysplasia and carcinoma of the uterine cervix (HPV), other skin squamous cell carcinomas, and Kaposi sarcoma (human herpes virus 8) [1,2]. Furthermore, studies have shown 4- to 10-fold increased incidence of genitourinary cancer in kidney transplant recipients [1–3]. Because polyomavirus and papillomavirus have tropism for genitourinary tissue, these entities deserve further consideration in the context of genitourinary cancers.

The human polyomavirus family includes JC virus and BK virus, which share structural similarities with the simian virus SV40 [4]. It is estimated that 90% of the general population are infected asymptomatically by polyomavirus BK during childhood [5]. Upon resolution of the primary infection, the virus persists in the genitourinary tract throughout adulthood in a latent state. In the setting of immunosuppression, the virus can be reactivated and cause polyomavirus-associated nephropathy, ureteral stenosis, or hemorrhagic cystitis, which can lead to allograft loss in the setting of renal transplant [6]. Indeed, approximately 30% of renal transplant patients show polyomavirus BK reactivation [5].

The oncogenic potential of polyomavirus in human urinary tract has been demonstrated in both human cell lines and animal models [7]. However, the role and oncogenic mechanism of polyomavirus in the development of genitourinary cancer in kidney transplant patients remains unclear. Polyomavirus-associated urothelial carcinoma (UC) in renal transplant patients has been investigated in previous case reports or small series [8–19] . To date, 3 case reports of polyomavirus-positive renal carcinoma in transplant patients have been published; however, these were all poorly differentiated carcinomas, without demonstration of typical renal cell differentiation, and could nevertheless represent poorly differentiated urothelial cell carcinoma, or collecting duct carcinoma [20–22].

In addition to polyomavirus, the prevalence of HPV in bladder cancer in the general population has been investigated but has shown great variability [23]. Although there is known association of HPV with anal and cervical dysplasia in transplant recipients, the very limited studies on the prevalence of HPV-associated bladder cancer in transplant populations have not been conclusive [24–27].

We reviewed the genitourinary cancers in kidney transplant recipients at our center from the past 20 years and investigated the presence of polyomavirus large T antigen and HPV by immunohistochemistry and in situ hybridization (for high-risk HPV), in correlation with clinical parameters and long-term outcome.

2. Materials and methods

With institutional review board approval, pathology records of Oregon Health & Science University were searched for genitourinary cancer in kidney recipients transplanted from 1994 to 2014, using keywords including transplant, allograft, in combination with bladder carcinoma, UC, renal cell carcinoma (RCC), or prostate adenocarcinoma. This search was supplemented by data from the clinical transplant database. We identified 20 genitourinary cancer cases in 16 patients including 13 bladder/ureter carcinomas, 5 RCCs, and 2 prostate cancers. Histologic slides were reviewed by 2 pathologists (for 5 patients, a limited set of slides were available); clinical history and follow-up were obtained from electronic medical record review.

Four-micron unstained sections were prepared and immunostained with an SV40 large T antibody (clone PAB416 raised to amino acid epitope 83-128 from Calbiochem/Millipore [Darmstadt, Germany] after cc1 mild antigen retrieval, 1:400 dilution, 16-minute antibody incubation without heat, plus amplification step), or the p16 antibody (clone E6H4 [CINtech from Ventana, Tucson, AZ] after cc2 mild antigen retrieval, predilute antibody, incubated for 16 minutes without heat) using automated immunostainers with Ultraview (all Ventana) detection chemistry. Large T–positive cases were further tested at University of Pittsburgh Medical Center with an in situ hybridization method to detect BK polyomavirus sequences (Enzo Life Sciences [Farmingdale, NY]; probe derived from nick translation of the entire BK genome), according to the manufacturer's protocol [28]. p16-positive cases were further tested by in situ hybridization for HPV types 16 and 18 using the in situ hybridization method for Pathogene probes from Enzo on the BenchMark ULTRA stainer (Ventana) after cc2 mild antigen retrieval. Carcinomas were classified as HPV positive when blue signal was seen localized to the nuclei of tumor cells.

3. Results

3.1. Patients and transplants

Among 2345 kidney transplant patients in the past 20 years at our center, 16 patients with 20 genitourinary cancers (0.7%) were identified, including 2 patients with 2 types of genitourinary cancer (11 men, 5 women; Table 1). Patients had a mean age of 58 years (range, 31-86 years) at the time of cancer diagnosis. The interval between first kidney transplant and cancer diagnosis ranged from 5 to 21 years with a mean of 12.8 years. Four patients received a second allograft after failure of the first transplanted kidney, one of whom was retransplanted after cancer treatment (patient 10; Tables 1 and 2). The etiology of native renal failure was reported as reflux, obstruction or pyelonephritis (4 patients), diabetes (2 patients), hypertension (2 patients), membranoproliferative glomerulonephritis (1 patient), Goodpastures (1 patient), "chronic glomerulonephritis" (2 patients), and unknown (4 patients).