The Prevalence and Prognostic Significance of Polyomavirus Infection in Patients with Urothelial Carcinoma of the Bladder

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Purpose: Human polyomaviruses (PV) has been associated with oncogenicity; however, the association between human bladder cancer and PV remains inconclusive. Moreover, whether PV has the interaction with p53 in tumorigenesis and their prognostic significance on human bladder cancer has yet to be determined.

Materials and Methods: Bladder tumor specimens and clinical parameters from 74 patients with urothelial carcinoma were collected. Immunohistochemical analysis using monoclonal antibodies specific to PV large tumor antigen (TAg) and p53 protein was performed to investigate the involvement of PV in human bladder tumorigenesis and the prognostic significance of TAg and p53 expressions using Cox proportional hazards model.

Results: The mean age of the 74 patients at diagnosis was 64 years and 61 (82.4%) were male. The expression of PV TAg protein was found in 45 (60.8%) tumor samples, but was not correlated with the expression of p53 (P = .280). The detection of PV TAg was significantly associated with tumor stage (P = .001) but not decreased overall survival (OS) or cancer-specific survival (CSS) (P = .661 and .738, respectively). However, the p53 overexpression was significantly associated with decreased CSS (P = .028). In multivariate Cox proportional hazards analysis, age and p53 overexpression were predictors of OS (P = .026) independently of tumor stage and CSS (P = .042), respectively.

Conclusion: We found that PV, which was detected in a significant percentage of tumor specimens, may be an important co-factor in the tumorigenesis of the bladder in humans. However, only p53 overexpression was associated with predicting CSS independently of tumor stage.

Keywords: BK virus; large T Antigen; oncogenicity; polyomavirus; protein p53; survival; urinary bladder neoplasms

INTRODUCTION

Most humans become infected with human polyomaviruses (PV) during childhood, which then establishes a life-long latent infection, particularly in the kidneys and urinary tract.[1] Reactivation of the PV infection can occur in people with a compromised immune system, such as patients undergoing organ transplantation, which can lead to diseases like hemorrhagic cystitis and polyomavirus nephropathy.[2] PV, and mainly the BK virus (BKV), have been reported to be oncogenic viruses in many cell and animal studies.[3-5] The early region of PV encodes two known oncoproteins, large tumor antigen (TAg) and small tumor antigen (tAg), which may lead to transformation by interacting with cellular tumor suppression proteins, such as p53 and inhibiting protein phosphatase 2A, respectively.[6,7] Although an increasing number of recent studies have investigated the potential association between PV and various human tumors, the results are still inconclusive.[8] Bladder cancer is the most common malignancy involving the urinary system in developed countries, with urothelial carcinoma (UCC) being the predominant histologic type.[9] However, there is wide variation in the reported incidence in different regions.[10] Furthermore, the incidence of bladder UCC is significantly higher in patients with chronic kidney disease and those undergoing renal transplants, particularly in Asian countries.[11,12] These findings imply that the contributory factors for bladder tumorigenesis are complex. Considering that PV is known to persist in the urinary tract and can be reactivated in immunocompromised people, it is reasonable to hypothesize that urinary tract carcinomas are likely to be associated with PV, particularly in Asian countries. To date, few studies with a small number of patients have discussed the association between PV and the development of human bladder UCC and the interaction with p53 in tumorigenesis. In addition, it is unclear whether PV infection has an impact on tumor grade, tumor stage and clinical prognosis of bladder cancer. Therefore, the aim of this study was to investigate the involvement of PV in human bladder tumorigenesis and clarify the prognostic significance of PV

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Table 1. Relationships between PV TAg immunostaining, p53 expression and clinicopathological parameters in patients with urothelial carcinoma of the bladder.

Variables[a]	Total (N = 74)	PV TAg Immunostaining		*P* Value
		Positive (N = 45)	Negative (N = 29)	
Age at diagnosis (years)	64.5 ± 14.8	66.1 ± 12.1	62.2 ± 18.4	.325
Gender				
Male	61 (82.4%)	38 (84.4%)	23 (79.3%)	.571
Female	13 (17.6%)	7 (15.6%)	6 (20.7%)	
Ever-smoker[b]	37 (54.4%)	23 (51.1%)	14 (48.2%)	.812
Tumor grade				
Low	2 (2.8%)	0 (0.0%)	2 (6.9%)	.074
High	72 (97.2%)	45 (100.0%)	27 (93.1%)	
Tumor stage				
0a or 0is	13 (17.5%)	4 (8.9%)	9 (31.0%)	.001
I	33 (44.6%)	22 (48.9%)	11 (37.9%)	
II	10 (13.5%)	3 (6.7%)	7 (24.1%)	
III	14 (18.9%)	14 (31.1%)	0 (0.0%)	
IV	4 (5.5%)	2 (4.4%)	2 (6.9%)	
p53 immunostaining				
Positive	56 (76%)	36 (80%)	20 (69%)	.28
Negative	18 (24%)	9 (20%)	9 (31%)	

Abbreviations: PV TAg, polyomaviruses large tumor antigen
aData are shown as numbers with percentage or means ± standard deviation
bData in six patients were missing

TAg and p53 expressions on human bladder cancer.

MATERIALS AND METHODS

Study Population

A total of 74 formalin-fixed and paraffin-embedded tumor samples were obtained from 74 patients with a diagnosis of UCC of the bladder at Chung Shan Medical University and Changhua Christian Hospital after the local institutional review board approved this study (CS11140). All tumors were retrospectively re-graded and re-staged according to the 2010 American Joint Committee on Cancer (AJCC) staging system by an experienced pathologist.[13] The study included 61 male and 13 female patients with a mean age of 64.5 years. The mean follow-up period was 53 months.

Procedures

Paraffin-embedded tumor tissue sections (4-μm) on poly-1-lysine-coated slides were deparaffinized. After treatment with 3% H_2O_2 in methanol, the sections were hydrated with gradient alcohol and PBS, incubated in 10 mM citrate buffer and finally heated at 100 °C for 20 minutes in PBS. The immunohistochemical procedure for the monoclonal antibody to SV40 TAg (Oncogen Research Products, Cambridge, MA) followed standard immunoalkaline phosphatase methods and was preceded by pressure-cooked antigen retrieval for 5 min in Ventana retrieval buffer (pH 10.0; Ventana Medical Systems, Tucson, AZ). Diaminobenzidine tetrahydrochloride was used as a chromogen. The monoclonal antibody was used to detect epitopes unique to PV TAg and shared by SV40, BK, and JC viruses. For p53 detection, the sections were heated in a microwave oven twice for 5 min in citrate buffer (pH 6.0), and then incubated with a monoclonal antihuman p53 antibody (DAKO, DO7; at a dilution of 1:250) for 60 min at 25°C. The conventional streptavidin peroxidase method (DAKO, LSAB Kit K675) was used to develop signals, and the cells were counterstained with hematoxylin.

Evaluations

The intensities of signals were evaluated independently by two observers. Negative immunostaining for p53 protein was defined as 0% to 10% positive nuclei and >10% positive nuclei was defined as positive for immunostaining (overexpression).[14] In addition, any positive nuclear reaction to PV TAg was defined as positive staining. Positive control slides for p53 protein detection were purchased from DAKO and renal allograft tissues with BK virus infection were used as positive controls for PV TAg. A neutralizing peptide was used to replace antibodies and served as a negative control.

Statistical Analysis

Given a type I error (α) level of 0.05, type II error (β) level of 0.20, the prevalence of human PV among patients with UCC of 0.17,[15] the prevalence of human P53

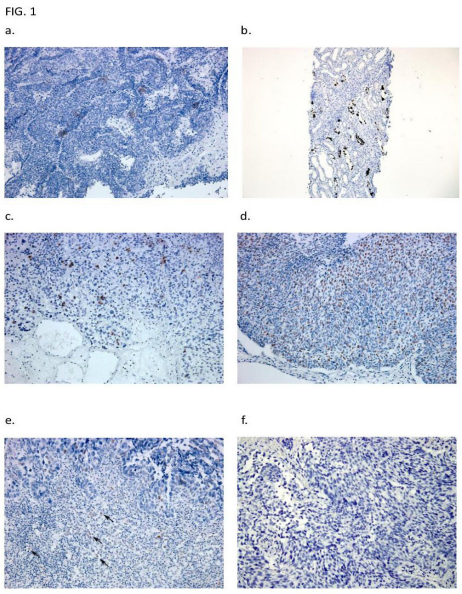

Figure 1. Immunohistochemical analysis of the PV TAg protein, using monoclonal antibody to SV40 TAg, in urothelial cell carcinoma of the bladder and adjacent normal tissues. **(a)** Negative results of PV TAg immunostaining in high-grade tumor cells (×100); **(b)** PV TAg protein expressed in renal allograft with PV nephropathy as a positive control (×100); **(c)** PV TAg protein expressed focally in high-grade tumor cells (×200); **(d)** PV TAg protein expressed diffusively in high-grade tumor cells (×200); **(e)** PV TAg protein expressed in few adjacent normal lymphocytes in high-grade tumor tissues (×200); **(f)** negative control of tumor tissues using antibody dilution buffer to replace the antibodies (×200).

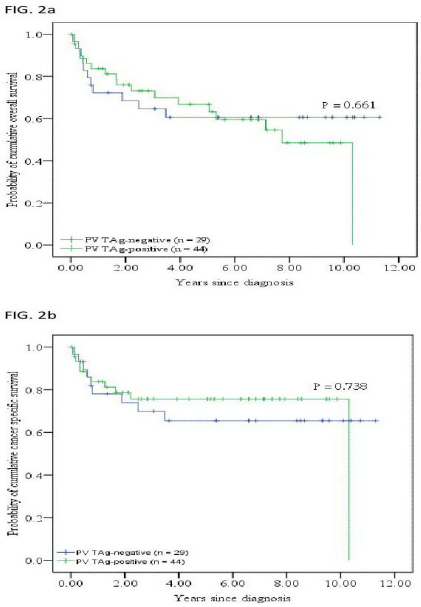

Figure 2. Kaplan–Meier post diagnostic survival curves. Overall survival **(a)** and cancer- specific survival **(b)** among the patients with urothelial carcinoma of the bladder, defined by the status of PV TAg expression.

among patients with UCC of 0.37,[14] detectable relative risks of 3.5, the minimum sample size required for each group was calculated to be 30. Additional subjects (nearly 20%) were recruited to avoid the loss to follow-up. Finally, we recruited a total of 74 patients in this study. The patients' age at diagnosis, gender, and smoking status were recorded. Overall survival (OS) was calculated as the period from the date of diagnosis to the date of death or the date of last follow-up. Cancer-specific survival (CSS) was defined as death attributable to bladder UCC. For categorical and continuous variables, Pearson chi-square and ANOVA tests were used to determine association between PV TAg expression and variables of interest. Kaplan-Meier analysis and the log-rank test/Gray's test were used to evaluate the associations between the expression of PV TAg and p53 with OS and CSS. A Cox proportional hazards model was used to evaluate the variables of interest in predicting OS and CSS. The combined effect of human PV TAg and p53 expressions on the survival of UCC patients was also evaluated. Interaction was further assessed using the likelihood ratio test to calculate X^2 and *P* values. In the test for interaction, the conditional logistic regression model with only main effects was compared to that with both main effect terms and interaction term. Values were expressed as mean ± SD. *P*-values of less than 0.05 were considered to indicate statistical significance. All analyses were performed using SPSS software for Windows version 12.0 (SPSS Inc., Chicago, IL).

RESULTS

Patients' Characteristics and Clinical Parameters

The patients' characteristics are shown in **Table 1**. Of the 74 patients, 25 (34%) received radial cystectomy with lymph node dissection. The final pathology of these 25 patients revealed that two had positive surgical margins, lymphovascular invasion, and positive lymph nodes; two had positive lymphovascular invasion and lymph node status; one had positive surgical margin; and one had positive lymphovascular invasion. At the end of study, 29 patients had died, of whom 20 had died from cancer-related deaths.

PV TAg Immunohistochemistry and Association with Clinical Parameters

Of the 74 bladder tumors, 45 (60.8%) had positive nuclear reactivity to PV TAg, which was only expressed in the tumor cells as well as a few adjacent normal lymphocytes in the tumor tissues (**Figure 1**). The relationships between the expression of PV TAg and clinical parameters of the patients with bladder UCC are shown in **Table 1**. The tumors that expressed PV TAg tended to be of a higher tumor stage than those that did not (*P* = .001). However, neither tumor grade nor p53 protein expression was associated with the expression of PV TAg (*P* = .258 and .280, respectively). The Kaplan-Meier curves for OS and CSS, defined by the status of PV TAg expression, are shown in **Figure 2a and 2b**. The OS and CSS between the patients with and without TAg expression in their bladder tumors were not statistically different in the Kaplan-Meier analysis (*P* = .661 and .738, respectively).

P53 Immunohistochemistry and Association with Clinical parameters

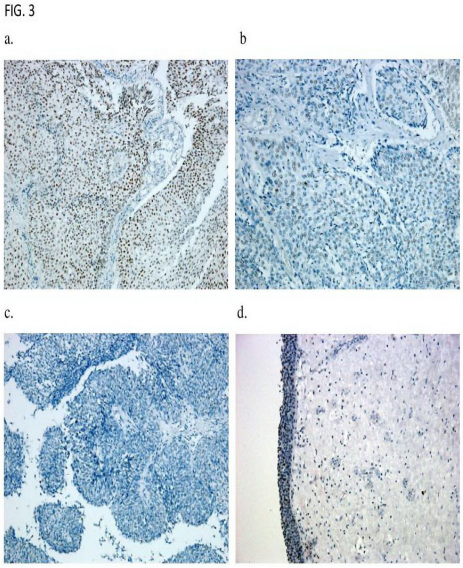

Figure 3. Immunohistochemical detection of p53 nuclear reactivity, using anti-p53 monoclonal antibodies in urothelial cell carcinoma of the bladder. **(a)** Diffuse positive staining (> 50%) in high-grade urothelial cell carcinoma (×100); **(b)** heterogeneous positive staining (10 to 50%) in high-grade invasive urothelial cell carcinoma (×100); **(c)** scattered positive staining in high-grade tumor cells (<10%) (×100); **(d)** non-tumor sample with scattered positive staining as a normal control (×100)

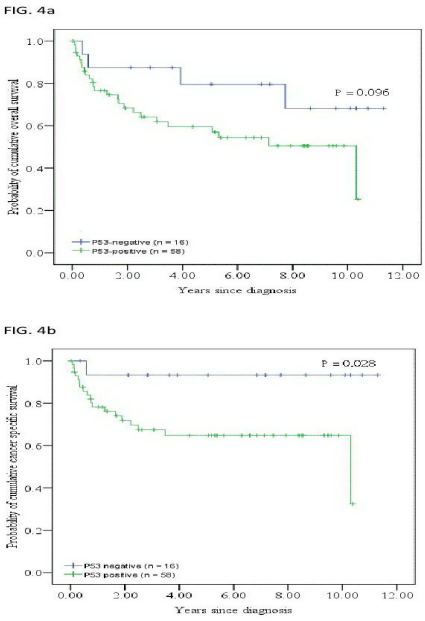

Figure 4. Kaplan-Meier post-diagnostic survival curves. Overall survival **(a)** and cancer-specific survival **(b)** among patients with urothelial carcinoma of the bladder, defined by the status of p53 expression

Although 56(76%) of the 74 bladder tumors demonstrated nuclear accumulation of p53 protein (**Figure 3**), neither tumor grade nor tumor stage was associated with the expression of p53 (P = .568 and .539, respectively). The Kaplan-Meier curves with Log-rank test for OS and CSS, defined by the status of p53 expression, are shown in **Figure 4a and 4b**. The patients with bladder UCC with p53 overexpression had significantly and borderline significantly worse CSS and OS (P = .028 and .096, respectively). Furthermore, the Gray's test was also used to compare the OS among the PV TAg-negative and PV TAg-positive patients and we found the two curves to be no significantly different (Gray's test result: $\chi^2 = 0.032$, df = 1, P = .859). A similar result was also found among the p53-negative and p53-positive group ($\chi^2 = 0.511$, df = 1, P = .612).

The Prognostic Significance of Variables of Interest in the Cox Proportional Hazards Model

The Cox proportional hazards model for predicting OS and CSS was adjusted for age, gender, tumor grade, tumor stage, smoking status, and the status of PV TAg and p53 expressions. The two independent factors predicting OS were age (95% confidence interval [CI]: 1.11 to 5.80, hazard ratio [HR] = 2.54, P = .026) and tumor stage (95% CI: 1.81 to 8.04, HR = 3.81, P < .001). The two independent factors predicting CSS were p53 overexpression (95% CI: 1.08 to 61.93, HR = 8.16, P = .042) and tumor stage (95% CI: 2.26 to 16.03, HR = 6.01, P < .001). Furthermore, no significant interaction between human PV TAg and P53 expressions on the OS of UCC patients was observed ($\chi^2 = 0.23$, P = .063).

DISCUSSION

Bladder cancer has a significant impact on health and medical costs because of its high incidence and prevalence in Chinese populations.[11,12] There are many established risk factors for bladder UCC, including male gender, smoking, exposure to various chemical carcinogens, and genetic factors.[16-20] Some infections, including chronic cystitis and human papillomavirus (HPV), have been associated with bladder cancer, although the findings are not consistent across the studies.[21,22] Even though PV is regarded to be an oncogenic virus because of its transformative behavior in vitro and in animal studies, few studies have reported an association between PV infection and the development of human bladder UCC.[15,23-30] In one Italian study, Monini et al.[24] reported that BKV DNA was detected in 15 (58%) of 26 bladder tumor tissues using the polymerase chain reactions (PCR). However, the prevalence of PV observed in a study from the U.S. with a larger sample size (76 patients), also using PCR, was only 5%.[29] In contrast to these studies using PCR, another study in the US using the immunohistochemical study reported a prevalence of PV in the 24 patients of nearly 17%.[15] The current study is the largest to date to investigate PV in bladder tumor samples, using immunohistochemistry (IHC), and we found PV TAg- positive rate in the bladder tumor samples of nearly 60%. The reason for this inconsistency in results between studies is unclear. In general, PCR has a greater degree of sensitivity than

IHC; however, it can also overestimate the prevalence of PV due to laboratory contamination. On the other hand, PCR may lead to the underestimation of the prevalence of PV due to the "hit-and-run" phenomenon. Another important issue is that even though we used a newer immunohistochemical technique (a streptavidin-biotin system, less non-specific background staining than with the conventional avidin-biotin complex method) with good quality control, we cannot exclude the possibility that the high prevalence of PV TAg positivity was caused, at least in part, by background staining. Although methodological differences and small sample sizes most likely explain the inconsistencies in the reported prevalence rates of PV in bladder tumor tissues, it is possible that ethnic and genetic variations in the susceptibility to PV carcinogenesis may be another possible explanation. In light of the high prevalence of PV in our bladder tumors, PV may be an important cofactor in human bladder tumorigenesis in Chinese patients. Previous studies have reported that PV TAg may exert its transformative activity by interacting with and functionally inactivating cellular p53 at a molecular level.[31,32] To elucidate whether TAg affects the expression of p53, we determined the expression of p53 in bladder tumor tissues using IHC. We found the expression of TAg was not associated with p53 expression, which implies that TAg probably inactivates p53 by binding directly to p53 without down-regulating its expression in bladder tumor tissues. Furthermore, we could not exclude the possibility that PV TAg mediates bladder tumorigenesis through other mechanisms, such as inactivating retinoblastoma susceptibility protein (pRb) or activating the insulin-like growth factor-I signaling pathway.[33,34] Recently, Alexiev et al. proposed that in the dysplastic background of p53 or pRb inactivation in BKV-infected urothelium, a "time lapse" may play an important role in tumorigenesis of bladder urothelial , which is consistent with the concept of multiple carcinogenesis casade.[35] To the best of our knowledge, this is the first study to report the relationships between the expression of PV TAg and clinical parameters of bladder UCC. The finding that the detection of PV TAg was significantly associated with tumor stage implies that PV infection affects the aggressiveness of a tumor, although further studies are needed to elucidate the mechanism. However, it is somewhat surprising that no associations were found between the expression of PV TAg and OS and CSS in Kaplan-Meir analysis. It may be attributable to inadequate power due to an insufficient sample size or heterogeneity of the study population. Further studies are needed to investigate the reasons for this discrepancy. It has been postulated that the overexpression of p53 implies a missense mutation of the p53 gene with a prolonged half-life, leading to nuclear accumulation of the mutant p53 protein, which can then be used as a prognostic predictor of bladder cancer.[14,36,37] Consistent with this hypothesis, we found that the overexpression of p53 was significantly associated with decreased CSS and borderline significantly with decreased OS in the Kaplan-Meir analysis. In the multivariate Cox proportional hazards model, p53 overexpression was an independent predictor of CSS. However, it is interesting to note that age rather than p53 overexpression was an independent predictor of OS. We think this may be explained by multiple comorbidities and poor performance in the elderly. Therefore, in treating patients with bladder UCC, it is important to consider age when choosing the therapeutic strategy.

CONCLUSIONS

In this study, PV was detected in a significant percentage of bladder cancer tissue samples, and may be an important cofactor in the tumorigenesis of human bladder and may also be associated with tumor stage. However, only the p53 overexpression was an independent predictor of CSS.

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