Urol Sci 2011;22(2):70–74

ELSEVIER

ORIGINAL ARTICLE

Urothelial Inverted Papilloma of the Lower Urinary Tract—A Benign Lesion or a Precursor of Malignancy?

Yi-Te Chiang, Junne-Yih Kuo*, Kuang-Kuo Chen, Yen-Hwa Chang, Howard H.H. Wu, William J.S. Huang

Division of Urology, Department of Surgery, Taipei Veterans General Hospital, and Department of Urology, School of Medicine, National Yang-Ming University, Taipei, Taiwan

Objective: We investigated the clinical characteristics and follow-up results of patients with a lower urinary tract inverted papilloma (IP) in our hospital, with the intention of clarifying whether certain groups require more aggressive surveillance.
Materials and Methods: We conducted a retrospective study of lower urinary tract IP, using the pathology database of Taipei Veterans General Hospital, from September 1992 to February 2008. In total, 67 patients were enrolled. Patients' clinical characteristics, symptoms, tumor locations, and follow-up data were analyzed.
Results: Among the 67 patients diagnosed with IP, 59 were male and eight were female, with a mean age of 67.9±12.4 years. Gross hematuria and lower-urinary-tract symptoms were the most common symptoms. All of the patients received transurethral resection as initial treatment. Thirty-eight of these patients were monitored for a median of 21 months (range: 3–168 months). Seven patients had synchronous urothelial malignancies, and one had recurrent IP during follow-up. No patient had subsequent urothelial carcinoma or IP recurrence without a synchronous or previous urothelial malignancy during follow-up.
Conclusion: There is a low incidence of developing a subsequent malignancy with a simple IP lesion during follow-up. Rigorous surveillance may be unnecessary in IP patients without a synchronous or previous urothelial malignancy.

*Corresponding author. Division of Urology, Department of Surgery, Taipei Veterans General Hospital, 201 Shih-Pai Road, Section 2, Taipei 11217, Taiwan.
E-mail: jykuotpe@hotmail.com

Received: April 23, 2010
Revised: May 14, 2010
Accepted: May 17, 2010

KEY WORDS:
benign urothelial tumor;
gross hematuria;
inverted papilloma

1. Introduction

An inverted papilloma (IP) is an uncommon urinary tract lesion that accounts for approximately 2% of all urothelial neoplasms.[1] It was first described by Potts and Hirst in 1963, and is characterized by a trabeculated pattern of proliferating urothelium that is arranged in inverted cords and nests.[2] Although an IP is usually regarded as a benign lesion based on histological findings, it sometimes causes obstruction in the upper urinary tract, and is found with a urothelial malignancy in some cases.[3–6] Therefore, the question of whether IP is a benign neoplasm or a precursor of malignancy remains, and the necessity of aggressive surveillance is also currently being debated.

At our hospital, we recommend that patients diagnosed with lower urinary tract IP (bladder and prostatic urethra) have regular cystoscopic monitoring. The aim of this study was to investigate the clinical characteristics and follow-up results of IP patients treated at our hospital, with the intention of clarifying whether certain groups require more aggressive surveillance.

2. Materials and Methods

From September 1992 to February 2008, we retrospectively identified 78 patients who were diagnosed with urinary tract IP lesions at Taipei Veterans General Hospital, and 67 patients were enrolled in this study. Among the patients, 38 had follow-up data after transurethral resection of IP. Patient characteristics (sex, age, initial symptoms, previous urinary tract malignancy, and initial diagnostic tool), tumor characteristics (multiplicity, site, and association with malignancy), and follow-up results were retrospectively analyzed. All histological slides were reviewed by uropathologists, and surveillance was performed using rigid cystoscopy approximately every 3 months. The follow-up period was defined as the time from diagnosis to the final cystoscopic examination.

3. Results

Sixty-seven patients were recruited for the study: 59 men and eight women, with a mean age at presentation of 67.9±12.4 years (range: 26–86 years). Nine (14%) of these patients had a history of previous urinary tract malignancy. Most patients presented with lower-urinary-tract symptoms or gross hematuria as the initial symptom (Table 1). Other patients had findings incidental to routine health examinations and previous genitourinary tract malignancies. The initial diagnostic tools for IP were cystoscopy and sonography in most patients. Other characteristics are listed in Table 1.

3.1. IP location

The locations of the lower urinary tract IP lesions are listed in Table 2. After transurethral resection of the bladder tumor, more than half (58%) of the IP lesions were located in the trigone and bladder neck.

3.2. Operative and follow-up results

Of the 67 lower urinary tract IP patients, eight (12%) had a synchronous malignancy: six with bladder cancer and two with renal pelvis cancer. Four patients (6%) had multifocal IP (2–4 tumors). Among these, two patients had IP combined with a synchronous renal pelvis urothelial carcinoma that was found at the time of surgery for IP; both patients underwent a nephroureterectomy and bladder cuff excision. One of the patients with invasive renal pelvis cancer died of the disease.

Follow-up data were available for 38 patients, and the median follow-up duration was 21 months (range: 3–168 months). These patients were divided into two groups according to their previous malignancy histories (Figure 1). In the group with a history of previous malignancy, one (12%) had a synchronous malignancy and recurrent pT1 bladder urothelial carcinoma 6 months after surgery. Another patient without a synchronous malignancy had IP recurrence 20 months after IP tumor removal. Of the six patients with a previous history of superficial cancer, one developed recurrent superficial bladder cancer 6 months after surgery and an invasive tumor 3 years later, and eventually died of the disease. The remaining five patients were free of disease during follow-up.

Of the 30 patients who had no history of urothelial malignancy, six (20%) had a synchronous urothelial malignancy that was found during surgery for IP. One of the six patients had invasive bladder cancer and succumbed to the disease soon after diagnosis. All of the remaining

Table 1 Patient and tumor characteristics in 67 patients with a lower-urinary-tract inverted papilloma[a]

Characteristic	*n* (%)
Sex	
Male	59 (88)
Female	8 (12)
Age (yr)	67.9±12.4 (26–86)
Previous urothelial malignancy history	9 (13)
Symptoms	
LUTS (e.g. dysuria, voiding difficulty)	28 (41)
Gross hematuria	17 (26)
Incidental finding during another operation (e.g. TURP)	9 (14)
During follow-up of a previous urothelial malignancy	7 (10)
Microhematuria	6 (9)
Initial diagnostic tools	
Cystoscopy	42 (63)
Sonography	15 (22)
Intravenous pyelography	6 (9)
Computed tomography	3 (4.5)
Magnetic resonance imaging	1 (1.5)

[a]Data are presented as *n* (%) or mean±standard deviation (range). LUTS=lower-urinary-tract symptoms; TURP=transurethral resection of the prostate.

Table 2 Tumor locations in 67 patients with a lower-urinary-tract inverted papilloma

Location	*n* (%)
Bladder	
Trigone	21 (31.2)
Bladder neck	18 (26.8)
Left lateral wall	6 (9.0)
Anterior wall	6 (9.0)
Right lateral wall	4 (6.0)
Posterior wall	4 (6.0)
Dome	2 (3.0)
Prostatic urethra	3 (4.5)
Not available	3 (4.5)

24 patients with no history of malignancy after IP surgery were disease-free during the follow-up period.

When looking for patients without a synchronous malignancy at diagnosis of bladder tumor, only one patient with a previous history of bladder cancer developed recurrent IP 20 months later. He remained disease-free for 2 years after his second transurethral resection to the time of his last follow-up. All four patients with multiple IP tumors were disease-free during follow-up (follow-up time: 11–69 months) except for one who soon died of invasive renal pelvis cancer.

4. Discussion

A brief review of IP studies is given in Table 3, with > 500 cases in the past two decades.[1,7–16] The largest study was done by Wan et al., and included 151 patients over the course of 12 years. They reported an incidence of 4.9% of IP among all bladder tumors.[10] Most IP tumors were found in patients aged 50–70 years. In our study, the mean age of IP patients was 67.9 years, which is consistent with other studies.[1,7–16] Juvenile IP has also been reported, with a clinical course similar to that in aged patients.[17] Our study also showed a predilection for males among our IP patients, with a ratio of men to women of 7.38: 1. In previous studies, the ratio was 6–10: 1.[1,7–16] Additionally, previous studies have indicated that the etiology of IP is associated with chronic inflammation, smoking, and other chemical agents.[10] Chan et al. have reported the presence of human papillomavirus type 18 in six of 10 IP patients, which suggests an oncogenic role in IP lesions.[18] Clarification of risk factors for IP still require studies with larger patient populations.

The most common symptoms of IP are lower-urinary-tract symptoms and gross hematuria, which also occurred among our patients (66%). Among our patients, 24% of the IP tumors were incidentally found on sonography or during endoscopic surgery such as transurethral resection of the prostate or ureteroscopy. Cystoscopy remains the most sensitive diagnostic tool and can help localize tumors. Imaging studies such as intravenous pyelography and computed tomography can be used for screening of the upper urinary tract for IP or other synchronous lesions. We did not submit urine cytology data because some of our patients had a history of previous malignancy. Typically, IP patients have negative urine cytology results because of its histological characteristics. Ho et al. have reported a 94% negative rate among 52 patients.[9] In a study by Witjes et al., 14% of patients had only mild atypia

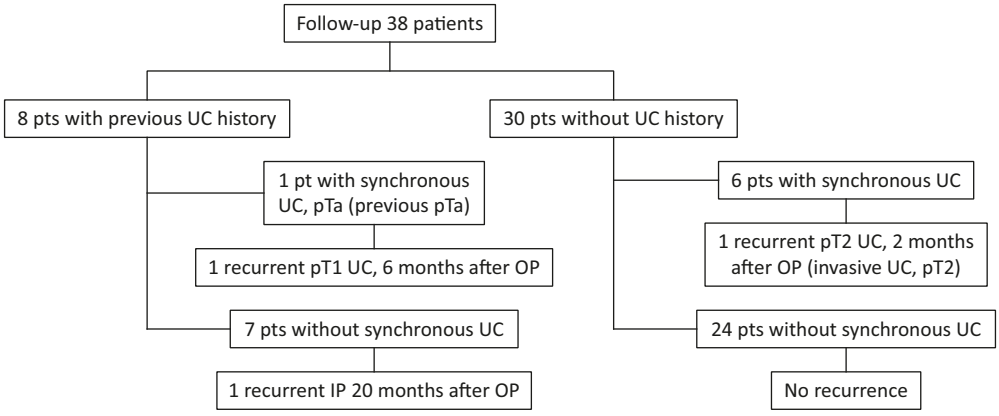

Figure 1 Follow-up results in 38 patients with lower-urinary-tract inverted papilloma. UC = urothelial carcinoma; OP = operation.

Table 3 Urinary tract inverted papilloma follow-up results in recent studies (with > 30 patients)

Reference	Year	No. of patients	Follow-up patient no.	Previous UC history	Synchronous malignancy	Recurrence of IP	Subsequent malignancy[a]
Witjes et al.[14]	1997	37	31	0	0	2	1
Cheville et al.[13]	2000	51	51	1	6	0	1
Asano et al.[12]	2003	48	42	1	5	1	2
Wan et al.[10]	2005	151	118	NA	NA	5	2
Ho et al.[9]	2006	52	52	0	0	0	1
Sung et al.[8]	2006	75	75	0	0	1	0
Seung et al.[16]	2010	53	53	3	1	0	0
Current study		67	38	8	7	1	0

[a]Patients with no previous malignancy history. UC = urothelial carcinoma; IP = inverted papilloma; NA = not available.

of the urothelium.[14] Therefore, cytology is of limited use among IP patients.

On cystoscopic imaging, IP presents as a smooth-surfaced, non-papillary lesion with a pedunculated or sessile appearance. Occasionally, IP is difficult to differentiate from other lesions, such as cystitis cystica, cystitis glandularis, and urothelial malignancies. The majority of IP lesions are found in the lower urinary tract, with an incidence of 80–95%.[1,7–16] In our study, we enrolled only patients with bladder and prostatic urethral IP, because of the ease of cystoscopic follow-up. Among our IP patients, the most common locations for IP were the trigone (31%) and bladder neck (27%), which are similar to those in other IP studies (50–80%).[1,7–16] Transurethral resection remains the standard treatment for IP lesions of the lower urinary tract.

In our study, most of the IP lesions occurred singly, but multiple lesions were found in four patients (6%). Our data are consistent with a study by Cheng et al., who have reported an incidence of multiplicity of 4.4% in a review of 322 patients with lower urinary tract IP.[11] Another review of 277 patients by Witjes et al. has reported an incidence of IP multiplicity of 5.4%.[14] In contrast, the chances of developing multiple IP tumors is much lower than that for urothelial carcinoma, which has a 35% rate of multiplicity.[19] Simultaneous presentation of a urothelial malignancy and IP has also been reported in previous studies.[1,7–16] In addition, eight patients (12%) had synchronous malignancies, and most of them had no previous history of urothelial malignancy. In a study by Asano et al., five of 48 patients (10%) had synchronous malignancies.[12] Larger studies have reported rates of simultaneous urothelial carcinoma and IP of 5.9–12%.[11–13] Importantly, half of the multiple IP patients in our study had a synchronous urothelial malignancy, which is much greater than the rate among patients with single IP lesions. We recommend that when multiple IP lesions are found, care should be taken to look for an accompanying synchronous malignancy.

Overall, we found that the characteristics of IP were benign owing to its low recurrence rate during follow-up. Only one of 38 patients developed recurrence of IP after 20 months of follow-up. That patient had a history of bladder cancer and was disease-free after a second transurethral resection of the bladder tumor. Twenty-four patients with no urothelial malignancy history or synchronous malignancy were disease-free during our follow-up. Sung et al. have reported that only one of 75 patients without a synchronous or previous urothelial malignancy developed recurrent IP, and no patient had a subsequent urothelial malignancy during follow-up.[8] Cheng et al. have reviewed 260 patients with lower-urinary-tract IP and have calculated a rate of subsequent urothelial malignancy of 2.7%.[11] Moreover, if those patients had no previous urothelial malignancy or synchronous malignancy, the incidence of subsequent urothelial malignancy was only 1.5%, which was significantly lower.[11]

Histologically, IP is a benign neoplasm with trabeculations of the urothelium and has an endophytic growth pattern. Henderson et al. have defined several criteria for diagnosis of IP lesions, including an inverted configuration, a covering layer of urothelium, uniformity of epithelial cells, absence or rarity of mitoses, formation of microcysts (crypts), and squamous metaplasia.[20] However, few cases of concurrent urothelial malignancy inside IP lesions or a urothelial carcinoma with an inverted growth pattern have been reported.[21] Additionally, IP lesions in the bladder could have focal papillary patterns.[22] The accuracy of the histopathological diagnosis is very important if IP lesions have atypical features or resemble a low-grade urothelial carcinoma. In a study by Witjes et al., the misdiagnosis rate was 27% after reviewing histological slides for which most of the misdiagnoses were actually low-grade urothelial malignancies.[14] The accuracy of the results also influences patient treatment plans and surveillance. Several immunohistochemical stains can help to distinguish between these lesions. Cytokeratin 20, p53, and Ki67 are the most common immunohistochemical markers that are increased in urothelial carcinoma.[23–25] Broussard et al. have evaluated 11 atypical IP cases using these immunohistochemical stains.[26] They have found no significant increases in these markers in IP lesions, which indicates no association between IP and urothelial carcinoma based on the markers. To predict further malignant changes, Urakami et al. have reported that when IP lesions have high immunoreactivity for proliferating cell nuclear antigen, p53, and intense Feulgen staining, the lesions are more susceptible to malignant transformation, because of the high proliferative activity.[27]

With the advancement of molecular analyses, Lott et al. have reported that among 78 IP lesions, none developed mutations of the tumor suppression gene, Tp53, which supports the concept that IP lesions differ from urothelial malignancies.[28] Sung et al. also have analyzed IP lesions with several polymorphic microsatellite DNA markers in which alterations frequently occur in urothelial carcinoma.[29] They have reported that the incidence of loss of heterozygosity in these markers is low, which differs from urothelial carcinoma. In a study by Eiber et al., which has combined histopathological and molecular analyses, IP lesions lacked specific genetic alterations, and the rate of aberrant immunostaining was low compared to that of urothelial carcinoma with a prominent inverted growth pattern.[30] These studies have strongly supported our hypothesis that IP is more likely a benign lesion rather than a malignancy. Furthermore, Jones et al. have used fluorescence *in situ* hybridization, immunohistochemistry, and morphological analysis to differentiate inverted urothelial carcinomas and IP lesions.[21] All of the IP lesions had normal results compared to a 72% positive rate for urothelial carcinomas with an inverted growth pattern. The UroVysion fluorescence *in situ* hybridization test was useful in distinguishing between these lesions. It provided further evidence that IPs and urothelial

carcinomas are phenotypically and genotypically distinct neoplasms.

Although we believe that IP is a benign neoplasm, several strengths and limitations of this study deserve comment. First, this was a retrospective study, and some of our patients were lost to follow-up. We usually performed rigid cystoscopy; therefore, some patients may have been afraid of the discomfort associated with the examination and thus been unwilling to participate in follow-up. Second, patients with multiple IPs were extremely rare; therefore, we could not determine whether these patients were prone to a concurrent urothelial malignancy. A study with a larger patient population should be carried out to validate our findings. Third, we did not have direct evidence to prove that subsequent bladder cancer had no correlation with previous IP lesions. Further histopathological research is needed.

We suggest that patients with IP receive regular surveillance. For a patient with a simple IP lesion, previous studies have suggested a 3-month or biannual cystoscopic examination,[11,12] but recent studies have recommended less rigorous surveillance because of its benign characteristics.[8,9] A 6-month or longer period between cystoscopic examinations may be sufficient.

In summary, IP is a benign lesion rather than a precursor of malignancy. Our study demonstrated that patients with a simple IP lesion had a low incidence rate of developing a subsequent malignancy. Rigorous preventive interventions may be unnecessary in IP patients without a synchronous or previous urothelial neoplasm.

References

1. Tsujimura A, Oka T, Miki T, et al. Clinical studies of inverted papilloma of the bladder. *Hinyokika Kiyo* 1996;42:423–6.
2. Potts IF, Hirst E. Inverted papilloma of the bladder. *J Urol* 1963;90: 175–9.
3. de Diego Rodriguez E, Villanueva Pena A, Hernandez Castrillo A, Gomez Ortega JM. Secondary obstructive uropathy to inverted papilloma of the ureter. *Actas Urol Esp* 2005;29:507–10. [In Spanish]
4. Cosgrove DJ, Monga M. Inverted papilloma as a cause of high-grade ureteral obstruction. *Urology* 2000;56:856.
5. Hoekx L, Wyndaele JJ. Bilateral ureteral inverted papilloma with synchronous transitional cell tumor of the bladder. *Acta Urol Belg* 1998;66:17–9.
6. de Knijff DW, Theunissen PH, Delaere KP. Inverted papilloma of the ureter with subsequent invasive bladder cancer. *Acta Urol Belg* 1997;65:45–6.
7. Kilciler M, Bedir S, Erdemir F, Ors O, Kibar Y, Dayanc M. Evaluation of urinary inverted papillomas: a report of 13 cases and literature review. *Kaohsiung J Med Sci* 2008;24:25–30.
8. Sung MT, Maclennan GT, Lopez-Beltran A, Montironi R, Cheng L. Natural history of urothelial inverted papilloma. *Cancer* 2006;107: 2622–7.
9. Ho H, Chen YD, Tan PH, Wang M, Lau WK, Cheng C. Inverted papilloma of urinary bladder: is long-term cystoscopic surveillance needed? A single center's experience. *Urology* 2006;68:333–6.
10. Wan Q, Luo JD, Cai SL, et al. Inverted urothelial papilloma: report of 151 cases. *Zhonghua Wai Ke Za Zhi* 2005;43:105–7. [In Chinese]
11. Cheng CW, Chan LW, Chan CK, et al. Is surveillance necessary for inverted papilloma in the urinary bladder and urethra? *Aust NZ J Surg* 2005;75:213–7.
12. Asano K, Miki J, Maeda S, Naruoka T, Takahashi H, Oishi Y. Clinical studies on inverted papilloma of the urinary tract: report of 48 cases and review of the literature. *J Urol* 2003;170:1209–12.
13. Cheville JC, Wu K, Sebo TJ, et al. Inverted urothelial papilloma: is ploidy, MIB-1 proliferative activity, or p53 protein accumulation predictive of urothelial carcinoma? *Cancer* 2000;88:632–6.
14. Witjes JA, van Balken MR, van de Kaa CA. The prognostic value of a primary inverted papilloma of the urinary tract. *J Urol* 1997;158: 1500–5.
15. Mattelaer J, Leonard A, Goddeeris P, D'Hoedt M, Van Kerrebroeck P. Inverted papilloma of bladder: clinical significance. *Urology* 1988; 32:192–7.
16. Lee SH, Mah SY, Chung BH. Incidentally discovered inverted papilloma of the urinary bladder in patients with lower urinary tract symptoms. *J Endourol* 2010;24:271–5.
17. Miyajima A, Mochizuki T, Seta K, Mizuguchi Y, Hayakawa M. Inverted papilloma arising in a juvenile. *Urol Int* 2000;65:60–2.
18. Chan KW, Wong KY, Srivastava G. Prevalence of six types of human papillomavirus in inverted papilloma and papillary transitional cell carcinoma of the bladder: an evaluation by polymerase chain reaction. *J Clin Pathol* 1997;50:1018–21.
19. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodriguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. *J Urol* 2000;163:73–8.
20. Henderson DW, Allen PW, Bourne AJ. Inverted urinary papilloma: report of five cases and review of the literature. *Virchows Arch A Pathol Anat Histol* 1975;366:177–86.
21. Jones TD, Zhang S, Lopez-Beltran A, et al. Urothelial carcinoma with an inverted growth pattern can be distinguished from inverted papilloma by fluorescence *in situ* hybridization, immunohistochemistry, and morphologic analysis. *Am J Surg Pathol* 2007;31:1861–7.
22. Albores-Saavedra J, Chable-Montero F, Hernandez-Rodriguez OX, Montante-Montes de Oca D, Angeles-Angeles A. Inverted urothelial papilloma of the urinary bladder with focal papillary pattern: a previously undescribed feature. *Ann Diagn Pathol* 2009;13:158–61.
23. Kilicli-Camur N, Kilicaslan I, Gulluoglu MG, Esen T, Uysal V. Impact of p53 and Ki-67 in predicting recurrence and progression of superficial (pTa and pT1) urothelial cell carcinomas of urinary bladder. *Pathol Int* 2002;52:463–9.
24. Harnden P, Eardley I, Joyce AD, Southgate J. Cytokeratin 20 as an objective marker of urothelial dysplasia. *Br J Urol* 1996;78:870–5.
25. Moll R, Lowe A, Laufer J, Franke WW. Cytokeratin 20 in human carcinomas. A new histodiagnostic marker detected by monoclonal antibodies. *Am J Pathol* 1992;140:427–47.
26. Broussard JN, Tan PH, Epstein JI. Atypia in inverted urothelial papillomas: pathology and prognostic significance. *Hum Pathol* 2004; 35:1499–504.
27. Urakami S, Igawa M, Shirakawa H, Shiina H, Ishibe T. Biological characteristics of inverted papilloma of the urinary bladder. *Br J Urol* 1996;77:55–60.
28. Lott S, Wang M, Zhang S, et al. FGFR3 and TP53 mutation analysis in inverted urothelial papilloma: incidence and etiological considerations. *Mod Pathol* 2009;22:627–32.
29. Sung MT, Eble JN, Wang M, Tan PH, Lopez-Beltran A, Cheng L. Inverted papilloma of the urinary bladder: a molecular genetic appraisal. *Mod Pathol* 2006;19:1289–94.
30. Eiber M, van Oers JM, Zwarthoff EC, et al. Low frequency of molecular changes and tumor recurrence in inverted papillomas of the urinary tract. *Am J Surg Pathol* 2007;31:938–46.