Original Article

Inverted papilloma of the urinary bladder: Rigorous surveillance needed? An Indian experience

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Abstract

AIMS: Inverted papilloma (IP) is an uncommon benign neoplasm of the urinary tract. Its multiplicity, recurrence, and association with transitional cell carcinoma (TCC) leads to conflicting clinical conclusions regarding its biological behavior, and hence, the need for rigorous follow-up protocols. In this study, we review all cases of urinary bladder IP in our institution and determine the need for strict follow-up. **MATERIALS AND METHODS:** We included consecutive patients from August 2004 to August 2008 with IP of the urinary bladder in this study who did not have prior or concurrent urothelial carcinoma. A single pathologist performed the histologic review. The patients had undergone strict a follow-up schedule every 6 months. **RESULTS:** In our study of the 24 patients, the mean age at presentation was 53.5 (range 22–81) years. The mean follow-up period was 25.8 months (range 6–58 months). Of the 24 patients, 21 were men and 3 were women. No patient had a synchronous or previous bladder tumor. The most common presenting symptoms were macroscopic hematuria and dysuria. All were solitary tumors except one, most commonly found at the bladder neck and trigone. The average follow-up period was 2.5 years without any evidence of recurrence. **CONCLUSIONS:** We conclude that when diagnosed by strictly defined criteria, IP as benign urothelial neoplasm was with extremely low incidence of recurrence and good prognosis. It does not seem to be a risk factor for TCC, especially if located in the bladder. Therefore, a good transurethral resection is adequate therapy and follow-up protocol as rigorous as those for TCC may not be necessary.

Key words: Bladder, inverted papilloma, surveillance protocol

Introduction

Bladder tumors are commonly occurring urologic tumors. The most common type of bladder tumor is urothelial carcinoma.[1]According to the WHO classification, urothelial tumors are divided into 4 major categories, namely, papilloma, papillary urothelial neoplasm of low malignant potential (LMP), low-grade and high-grade urothelial carcinoma, and noninvasive urothelial neoplasias.[2] Noninvasive urothelial neoplasms consist of carcinoma in situ, urothelial dysplasia, nephrogenic adenoma, and inverted urothelial papilloma, and so on[3] [Table 1]. Many cases of IP have been reported since first description of this entity by Potts and Hirst in 1963.[4] Inverted papilloma (IP) is an uncommon tumor

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Table 1: 2004 WHO classification of noninvasive urothelial neoplasia

Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial carcinoma *in situ*
Urothelial papilloma
Urothelial papilloma, inverted type
Papillary urothelial neoplasm of low malignant potential
Noninvasive low-grade papillary urothelial carcinoma
Noninvasive high-grade papillary urothelial carcinoma

of the urinary tract, accounting for about 2.2% of tumors of the urinary system and mostly occur in the fifth–sixth decade of life.[5] The clinical features are not specific and urothelial carcinoma shares similar endoscopic and radiologic appearances with IP.[4] IP of the urinary tract mostly occurs as a solitary lesion, but 3.6–6.0% appears to be multicentric.[6] In general, IP is considered to be a benign lesion. The benign clinical course of IP is based on its histologic appearance, low incidence of multiple tumors, low rate of local recurrence, and a lack of invasive growth and metastasis.[5,6] Although IP is traditionally regarded as a benign tumor, conflicting data on its multiplicity, recurrence rates, and association with urothelial carcinoma have left uncertainties concerning its biologic behavior.[7,8] In this study, we evaluated 24 cases with IP of the lower urinary tract, along with the relevant literature to know its biological behavior, relation to urothelial carcinoma, and to determine the need for strict follow-up.

Materials and Methods

From 2004 to 2008, 24 patients with urothelial IP of the lower urinary tract were treated in our hospital [Table 2]. The patients were evaluated for the following patients' characteristics (including age at presentation, sex, presenting symptoms), cystoscopic findings (including tumor location, size, and multiplicity), smoking history, urine cytology and associated urothelial neoplasm, and management (including treatment and follow-up status); some of the details were obtained from their medical records. All the slides were reviewed and diagnosed and those with no prior or concurrent urothelial carcinoma or carcinoma *in situ* were included in the current study. All patients were evaluated preoperatively by physical examination, ultrasonography (US), urine cytology, hematologic and biochemical analyses, and preoperative cystoscopy. Five of our patients were nonsmokers and the rest had long history of smoking. None of the patients had a history of previous bladder tumor. All the patients underwent transurethral resection of the bladder tumors (TURBT). Histopathologic diagnosis was carried out according to the criteria of Henderson *et al*[9] [Table 3]. The follow-up consisted of cystoscopy, ultrasound evaluation, and urine cytology every 6 months up to 2 years and then annually up to 5 years.

Table 2: Patients and tumor characteristics in patients of inverted papilloma bladder

Case	Year	Age	Sex	Location	Symptoms	Size	No.	Treatment	Recurrence	Smoking history	Follow-up (months)
1	1995	64	M	BN	HEMATU	0.5 × 0.5	S	TURBT	None	POS	22
2	1995	60	M	BN	HEMATU	1 × 1.5	S	TURBT	None	POS	25
3	1997	32	M	LL	HEMATU	1 × 1	S	TURBT	None	POS	30
4	1998	62	F	BN	HEMATU	0.5 × 1	S	TURBT	None	NEGAT	12
5	1998	64	M	TRIG	STOR SYM	0.5 × 0.5	S	TURBT	None	POS	8
6	1998	28	M	TRIG	DYS	1 × 2	S	TURBT	None	POS	35
7	1999	55	M	BN	HEMATU	1 × 1	S	TURBT	None	POS	24
8	1999	38	M	BN	DYS	1 × 0.5	S	TURBT	None	POS	30
9	1999	68	M	RL	BOO	2 × 1	S	TURBT	None	POS	28
10	2000	25	F	POST	HEMATU	1 × 1	S	TURBT	None	NEGAT	6
11	2000	30	M	BN	HEMATU	1 × 0.5	S	TURBT	None	POS	34
12	2001	55	M	TRIG	HEMATU	1 × 2	S	TURBT	None	NEG	40
13	2002	45	M	DOME	DYS	1 × 0.5	S	TURBT	+	POS	13
14	2002	81	M	BN	HEMATU	0.5 × 1	S	TURBT	None	POS	Lost
15	2002	22	M	BN	HEMATU	1.5 × 1	M	TURBT	None	POS	Lost
16	2002	68	M	BN	DYS	1 × 1	S	TURBT	None	NEG	18
17	2004	53	M	POST	ASYMP	1 × 1	S	TURBT	None	POS	38
18	2004	60	M	TRIG	STOR SYM	1 × 1	S	TURBT	None	POS	18
19	2005	43	M	BN	HEMATU	0.5 × 0.5	S	TURBT	None	POS	28
20	2006	77	M	BN	HEMATU	1 × 1	S	TURBT	None	NEG	24
21	2006	48	M	BN	HEMATU	1.5 × 2	S	TURBT	None	POS	40
22	2007	72	F	BN	DYS	1 × 0.5	S	TURBT	None	NEG	22
23	2008	65	M	TRIG	DYS	0.5 × 0.5	S	TURBT	None	POS	20
24	2008	69	M	BN	BOO	1 × 1	S	TURBT	None	POS	42

M, male; F, female; BN, bladder neck; TRIG, trigone; POST, posterior wall; RL, right lateral; LL, left lateral; DOM, dome; STOR, storage; SYM, symptoms; DYS, dysuria; BOO, bladder outlet obstruction; ASYMP, asymptomatic; HEMATU, gross hematuria; S, single M, multiple; TURBT, transurethral resection of bladder tumors; POS, positive; NEG, negative.

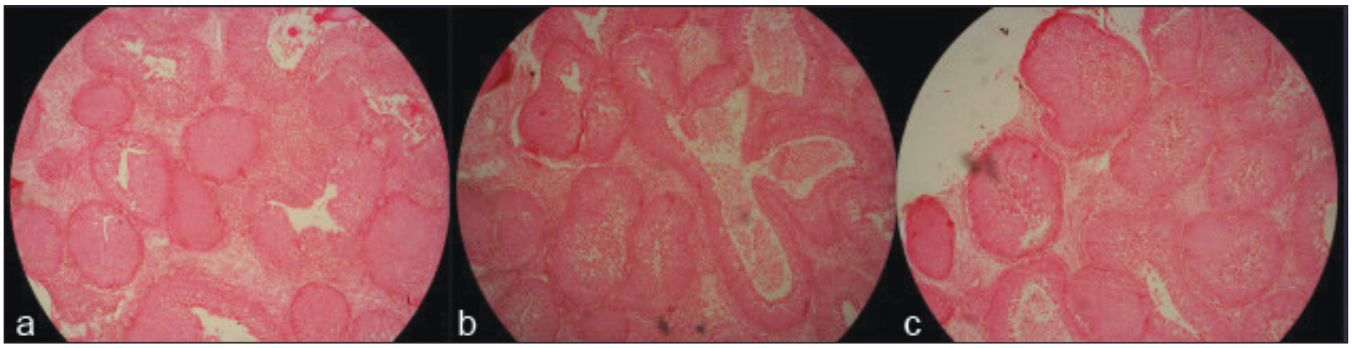

Figure 1: Low-power view showing distinct inverted growth pattern of papillary fronds of typical inverted papilloma composed of intact surface bladder urothelium (H and E, ×10)

Table 3: Diagnostic criteria for inverted papilloma[9]

Inverted configuration
Covering layer of urothelium
Uniformity of the epithelial cells
Absence or rarity of mitoses
Formation of microcysts (crypts)
Presence of squamous metaplasia

Results

In our study, the mean age of the patients was 53.5 (range 22–81) years. The mean follow-up period was 25.8 months (range, 6–58 months). Of the 24 patients, 21 were men and 3 were women. The physical findings were unremarkable in all the patients except in 2 in whom the bladder was palpable because of clot retention. Another 2 presented with acute urinary retention because of benign prostatic hyperplasia, with IP diagnosed during the transurethral resection of prostate. We selected only those cases in which the site of development of IP was the bladder. Initial symptoms included macroscopic hematuria in 9 cases of which 3 presented with clot retention, 2 with microscopic hematuria, 4 with dysuria, 2 with dysuria and microscopic hematuria, and 2 with bladder outlet obstruction; and 2 cases were asymptomatic and were diagnosed incidentally during an ultrasound examination for unrelated complaints. There was no history of urothelial carcinoma in any patient. Urine cytology was essentially noncontributory in these cases. Cystoscopy showed a polypoidal tumor in the bladder in 11 patients and sessile tumors in the remaining. All cases of IP were solitary and confined to urinary bladder except in 1 case in which multiple small tumors were present. Of these bladder tumors, 14 (58%) were in the bladder neck, 5 (20%) were on the trigone, 2 (8%) on the posterior wall, 1 each (4%) on the left and right lateral walls, and 1 (4%) was on the dome

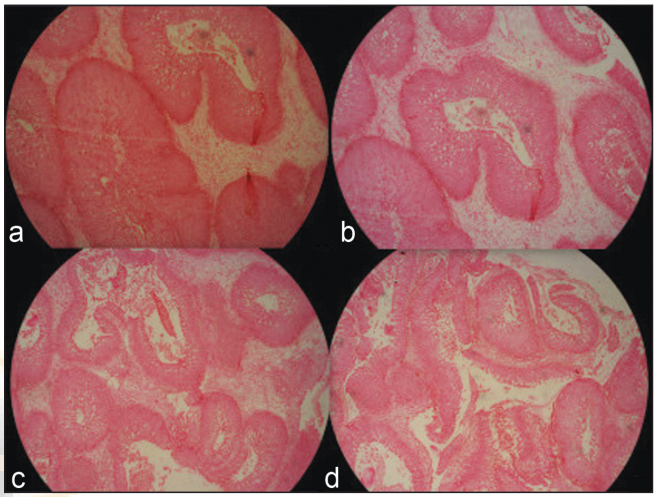

Figure 2: High-power view showing inverted growth pattern of lining cells with central streaming and peripheral palisading without any atypia and mitosis (H and E, ×40)

[Table 3]. TURBT was performed in all the cases. No postoperative complication occurred. The follow-up period defined as from diagnosis to the last cystoscopy evaluation. The follow-up data were available for all the patients except for 2. The patients were followed up for 2.5 years without any evidence of recurrence. The typical histologic appearances of IPs are shown in Figures 1 and 2.

Discussion

Although the term inverted papilloma was initially introduced in 1963 by Potts and Hirst to describe this architecturally distinctive urothelial neoplasm,[4] the Viennese urologist Paschkis had previously reported 4 morphologically identical urothelial tumors in 1927 under the name of adenomatoid polyp.[8] Many cases of IP have been reported since first description of this entity. IP of the urinary tract is an uncommon tumor that is usually regarded as benign and mostly occurs in the fifth–sixth decade of life, but it may occur at

any age, and some cases in children have also been reported.[10,11] The mean age of the patients in our study was 53 years showing a similar demographic trend. Inverted urothelial papillomas are more common in males than females. This unusually high male preponderance is out of line with other bladder tumors, since urothelial carcinoma has only a 2:1 male predominance.[12] In our series, the male-to-female ratio was 7:1 (21 vs 3). In other series, the male-to-female ratio ranged from 3:1 to 7:1.[6,8] Although these lesions are usually single, they may be seen as multiples.[13] Our data confirm these findings. The majority of IP cases occur in the bladder, and nearly 80% of the IP cases in the bladder are found in the neck or trigone region, whereas IPs of the lateral wall of bladder and dome are rare.[6] Among our cases, 80% developed in the bladder neck and trigone, which is consistent with previous reports. In the literature, the reported incidence of IP ranges between 1.6% and 4.5%.[14,15] During the period of the present study, the number of operations for bladder tumor in our hospital was 663 and the incidence of IP was 3.6%, similar to the levels reported by other investigators.[8] In addition, a significant number of patients in the current study (75%, 18 of 24 cases) had a smoking history, suggesting a possible link between tobacco smoking and IP. Although the relationship is inconclusive, perhaps it is worthy of further investigation.

The clinical significance of this entity remains controversial. Although IP has generally been regarded as a benign tumor in the epithelium of the urinary tract, centering on the bladder, several reported cases suggested the malignant potential of IP, including those with evidence of malignancy, those showing recurrences, and those with recurrence of urothelial carcinoma.[16] IP recurrence is rare, with a rate of 1–5.4%.[15] Incomplete tumor resection may contribute to the high recurrence rate. As such, we view IP recurrence with caution, especially if present in a similar location. In reviews of the published data, it was found that the median time to recurrence is not more than 2 years. In our cases, no recurrences have developed. However, it can still be difficult to differentiate this lesion from low-grade transitional cell carcinoma (TCC), cystitis cystica, cystitis glandularis, and Brunn's cell nests. Although the histologic distinction from lesions, such as cystitis cystica and cystitis glandularis do not affect the clinical outcome, it is necessary to differentiate IP from low-grade TCC, because the latter might recur and/or progress. Misdiagnoses are not uncommon and may represent 27% of the "initial" tumor diagnoses.[15

The relationship between IP and TCC is controversial. The association of IPs of the bladder and urothelial carcinoma has been well documented, but the incidence is low. Therefore, it is clinically prudent to exclude TCC when IP is diagnosed. In contrast, IPs of the upper urothelial tract frequently coexist with urothelial malignancies.[17] Spevack *et al* have maintained that the association between IPs and the urinary epithelial malignant tumors is more pronounced in the upper urinary tract and reported that 7 of 30 cases of the upper urinary tract IP were complicated with urothelial carcinoma.[18] In our study, there is no recurrence in about 2 years of follow-up. The etiology of IP is not yet clearly understood. In their first description of this lesion, Potts and Hirst suggested that an IP is a neoplastic transformation of basal cells of subcervical Albarran's or subtrigonal Home's glands.[4] Because IPs were later found outside the bladder, this idea seemed very unlikely.[18] Instead, Trites stated that this lesion was an inverted variant of the urothelial papilloma, a belief adopted by some others.[19] Matz *et al* postulated that this lesion was not neoplastic, but rather a kind of hyperplastic reaction, especially of Brunn's cell nests, to chronic inflammation or irritative agents.[20] This could explain the predominance in areas of greatest irritative potential, the rare multicentricity and the very low recurrence rate of IP. In recent years, this theory has been supported by others. Today, most authors believe that IP of the urinary tract is a true neoplasm, although the precise tissue of origin and the causative agents or processes are not yet known. Preoperative diagnosis of IP is difficult. There are no specific radiologic characteristics to support the diagnosis of IP. In our series, the most frequent abnormalities on US were bladder mass. Although sometimes US of the bladder may detect bladder mass, cystoscopy remains the diagnostic procedure of choice. Urine cytology has not been reported to be useful in aiding the diagnosis of urinary bladder IP. The shedding of cells is unlikely, when an intact layer of normal mucosa covers it. However, the presence of suspicious or malignant cells in urine cytology should alert the physician to the need for closer surveillance and re-evaluation of the histologic findings. With regard to the bladder tumors, endoscopy, direct visualization, and biopsy are the most frequent diagnostic procedures used to detect IPs.[8] Henderson *et al* defined 6 criteria for the diagnosis of IP[9] [Table 1]. In IPs, the tumor surface is cytologically unremarkable—generally intact, smooth, dome-shaped, and the ramifying cords are of even width. However, the surface of an urothelial carcinoma with inverted growth is sometimes exophytic and variable, and the ramifying cords and trabeculae have irregular widths, which are not characteristic features of IPs. Cell atypia, nuclear pleomorphism, irregularities of chromatin distribution, unusally high P53 accumulation or Ki67 counting, and an appreciable mitotic rate are the

prominent features in the diagnosis of urothelial cell carcinomas.[20] The coexistence of urothelial carcinoma and IP is well documented, although less commonly in the bladder. However, in our study, there was no coexistence of urothelial carcinoma at presentation. The associated clinical symptoms do not differ greatly from other urothelial neoplasms. There are no clinical criteria to differentiate IP from urothelial carcinoma. Approximately the same results were obtained from our cases. These tumors usually present with painless hematuria, dysuria, or bladder outlet obstruction, but they can be asymptomatic as demonstrated in one of our cases. Among our cases, 13 (54%) had gross hematuria, whereas 6 (25%) had dysuria. Today, we do not know of any reliable parameter that allows for the identification of patients with an increased risk of recurrence or malignant transformation. Some authors have suggested that human papillomavirus (HPV) may play a role in the pathogenesis of IP.[21] We carried out HPV analysis by microwave-based antigen retrieval method, which showed positivity for HPV 16 in 9 cases, including all female patients. The determination of DNA ploidy and the proliferative index may be useful for the appropriate management of this disease as it may affect further follow-up of patients. The typical gross appearance has been characterized as nonpapillary, noninvasive, smooth-surfaced, and pedunculated or sessile polypoid lesions of the urothelium.[8] The IPs range in size from a few millimeters to 3–4 cm in their greatest dimension, but most of them are smaller than 3 cm, as in our cases. Simple TURBT and/or electrocoagulation is generally accepted as the treatment of choice for IPs in the bladder.[8] In our series, all the patients with IPs in the bladder were treated with transurethral resection. Some authors do not advocate frequent and long-term follow-up because of rare multiplicity, very low recurrence rate, and absence of progression.[22-24]In contrast, most authors agree that patients with IP must be considered to be at risk for recurrence, and treatment should be followed-up with endoscopy and radiographic studies for recurrence.[25] Witjes *et al* concluded that IP was not a risk factor for urothelial carcinoma of the urinary tract, and frequent and long-term follow-up was not needed if the histologic diagnosis was definitive.[8] They had a single case of subsequent urothelial carcinoma development and 2 of IP recurrence. In contrast, cheng et al advised for regular cystoscopy during follow-up despite finding only a single case of subsequent urothelial cell carcinoma nearly 4 years after the initial diagnosis of IP.[26] Henry *et al* advised against the regular surveillance in histologically proven IP of bladder if there is no associated urothelial carcinoma.[25]

Recent molecular data support its benign nature based on the less number of genetic abnormalities found in most cases.[27] Such published results provide practicing urologists with conflicting information.

In conclusion, in our study, IPs in the urinary bladder, having both the extremely low Incidence of tumor recurrence and strikingly favorable Prognosis during follow-up suggest that inverted urothelial papilloma is a benign urothelial neoplasm, provided that the diagnosis of IP is based on strictly defined criteria. Consequently, trans-urethral resection of IP is adequate treatment, and surveillance protocols as rigorous as those employed in the management of urothelial carcinoma seem unnecessary for this benign entity. An initial diagnosis of IP should be challenged if progression is observed.

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