Transitional Cell Carcinoma of the Renal Pelvis

The Diagnostic Role of Pelvic Washings

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Key Words: Transitional cell carcinoma; Renal pelvis; Cytology; Urinary tract washings

Abstract

One hundred renal pelvic washings were reviewed blindly for 12 cytologic features. Of 52 washings with tissue confirmation, the cytologic diagnosis suggestive of or positive for transitional cell carcinoma (TCC) was made in 36 cases; 11 were negative, and 5 were unsatisfactory. Of 36 positive washings, histology confirmed the TCC diagnosis in 35 but revealed only reactive changes in 1. Of 11 negative washings, 9 were histologically negative for TCC, and 2 were positive for high-grade TCC. Among 48 washings without tissue confirmation, 33 were negative for TCC or showed reactive changes, 12 were negative for high-grade dysplasia or malignancy, but low-grade TCC could not be ruled out, 1 was suggestive of malignancy, and 2 were unsatisfactory. Clinical follow-up revealed no TCC. Predictive cytologic features of high-grade TCC were high nuclear/cytoplasmic ratio, isolated cells, anisonucleosis, nuclear hyperchromasia, and coarse chromatin; for low-grade they were presence of more than 5 papillary groups, cellular overlapping, anisonucleosis, and hyperchromasia. The sensitivity and specificity for the cytologic diagnosis were 89% and 97% for high-grade TCC and 100% and 78% for low-grade TCC, respectively.

Renal pelvic washings can be used to accurately diagnose TCC of the renal pelvis. The positive predictive value for high-grade TCC is 93%, but for low-grade tumors it is 43%.

Transitional cell carcinoma (TCC) of the upper urinary tract constitutes approximately 5% to 8% of all urothelial malignant neoplasms,[1-4] and TCC of the renal pelvis accounts for approximately 7% to 8% of all renal tumors.[2-10] Traditionally, the diagnosis of upper urinary tract TCC has been difficult and, until recently, relied on radiographic findings,[11] but the diagnostic role of urine cytology is being increasingly appreciated.

Urinary cytology is a frequently used and accepted method of diagnosing and following up patients with TCC of the urinary bladder.[1,11,12] However, voided urine is used less frequently and considered an insensitive method for diagnosing upper urinary tract TCC.[1,7,11,13] The low diagnostic yield is related to several factors, including the high frequency of low-grade TCC that exhibits only subtle nuclear atypia, the possible degeneration of tumor cells exfoliating from the upper tract through what may be a partially obstructed channel,[7] and the frequent presence of synchronous TCC in the urinary bladder.[13] In addition, the pelvic urothelium may intrinsically differ from its urinary bladder counterpart,[4,10,14,15] so that diagnostic criteria well recognized for urinary bladder TCC might not be readily applicable to that of the renal pelvis.

Better cytologic sampling of the upper urinary tract has been possible only recently with the introduction of flexible or small rigid ureteroscopes and instrumentation devices,[6] which enable direct visualization of the lesions for washing and brushing.[11] Yet, ureteral and renal pelvic specimens still raise some of the most challenging interpretation problems. Unlike the case for TCC of the urinary bladder, literature on the cytology of TCC of the upper urinary tract, including that of the renal pelvis, remains limited.[4,15] On the other hand, accuracy is critical since a diagnosis of TCC of the upper

Table 1
Evaluated Cytologic Features*

Feature	Positive for High-Grade TCC	Negative for High-Grade TCC; Rule out Low-Grade TCC	Negative
Papillary groups			
>5	64	100	33
>10	40	56	22
Umbrella cells	68	67	89
Increased nuclear/cytoplasmic ratio	100	67	33
"Hard" cytoplasm	68	67	33
Overlapping nuclei	68	89	44
Nuclear hyperchromasia	92	78	44
Nuclear pleomorphism	92	78	33
Individual atypical cells	100	67	22
Acute inflammation	64	44	33
Nucleoli	72	56	22
Cytoplasmic vacuolization	48	44	22
Coarse chromatin	92	67	33

TCC, transitional cell carcinoma.
* Diagnostic value expressed as percentage of washings in which features are present.

urinary tract often results in a major surgical procedure, including nephrectomy or nephroureterectomy.[3,4,14]

These considerations have prompted an attempt to determine the accuracy of renal pelvic washings in the diagnosis of TCC of the renal pelvis and to elucidate the cytologic criteria most useful for identifying low-grade and high-grade neoplasms.

Materials and Methods

Among 120 renal pelvic washing specimens obtained at the Methodist Hospital, Houston, TX, between January 1990 and June 1998, 20 were excluded from the study owing to a history of bacillus Calmette-Guérin or other chemotherapeutic treatments (15 washings in 3 patients) or the unavailability of slides for review (5 washings in 3 patients). The remaining 100 specimens were included in the study. They were derived from 54 patients, 38 men and 16 women, with ages ranging from 30 to 96 years. A final diagnosis was confirmed by biopsy, nephrectomy, or nephroureterectomy in 52 washings (32 patients) and by clinical follow-up in the remaining 48 washings (29 patients, 7 of whom also had contralateral renal pelvic washings with histologic confirmation).

The slides from each washing were reviewed blindly with special attention to 12 specific cytologic features: papillary transitional cell groups, "umbrella" cells, increased nuclear/cytoplasmic (N/C) ratios, "hard" cytoplasm, cellular overlapping, nuclear hyperchromasia, nuclear pleomorphism, individual dysplastic/malignant urothelial cells, acute inflammation, nucleoli, cytoplasmic vacuolization, and coarse chromatin **Table 1**. These features were recorded for each case as present or absent. Furthermore, papillary groups, when present, were graded according to the mean number calculated as the total number of groups/total number of slides per case: +, fewer than 5 groups; ++, 5 to 9 groups; and +++, 10 or more groups.

Each washing was originally classified into 1 of 5 diagnostic categories: (1) positive for high-grade dysplasia or TCC; (2) suggestive of high-grade dysplasia or TCC; (3) negative for high-grade dysplasia and TCC, low-grade TCC cannot be ruled out; (4) negative; and (5) unsatisfactory for evaluation. Subsequent review for this study showed that the positive washings (category 1; 19 cases) and the "suggestive" washings (category 2; 7 cases) shared the same cytologic spectrum and all of them, except 1, had tissue confirmation of high-grade TCC. As a result, these 2 categories were combined into the category positive. The cytologic diagnosis was compared with the final histologic diagnosis in the 52 washings in which tissue confirmation was available. TCC was diagnosed and graded according to a classification scheme proposed by the World Health Organization/International Society of Urologic Pathology.[16] In the remaining 48 washings, clinical follow-up was obtained by reviewing the medical records. Sensitivity, specificity, false-positive rates, and false-negative rates then were calculated for various diagnostic categories.

Results

Cases With Histologic Correlation

Of the renal pelvic washings, 52 (from 32 patients) had tissue confirmation. The cytologic-histologic correlation is shown in **Table 2**.

Table 2
Cytologic Diagnoses of 52 Renal Pelvic Washings With Tissue Correlation

	Histologic Diagnosis		
Cytologic Diagnosis (No. of Washings)	**High-Grade TCC**	**Low-Grade TCC**	**Negative**
High-grade TCC (n = 26)	25	0	1
Negative for high-grade TCC; rule out low-grade TCC (n = 10)	1	9	0
Negative (n = 11)	2	0	9
Unsatisfactory (n = 5)	2	1	2
Total (n = 52)	30	10	12

TCC, transitional cell carcinoma.

Of the 26 washings diagnosed as positive for high-grade TCC, histologic examination confirmed the presence of a high-grade TCC in 25 but failed to detect dysplasia or TCC of any grade in 1 case. The cytologic features found most helpful in making this diagnosis are illustrated in **Image 1**. These include individual neoplastic cells (seen in 100% of cases), increased N/C ratios (100%), nuclear hyperchromasia (92%), nuclear pleomorphism (92%), and coarse nuclear chromatin (92%). The single false-positive washing exhibited numerous papillary clusters (mean, >10/slide), with single cells characterized by increased N/C ratios, hyperchromasia, pleomorphism, coarse chromatin, and overlapping of the nuclei **Image 2**. Two other pelvic washings performed 14 days later were negative, showing none of the features of the previous washing. A biopsy of the renal pelvis at the time of the subsequent washings showed no diagnostic features of malignancy. One year later, a repeated washing was positive for TCC, and a nephroureterectomy showed TCC, grade II/III.

Of the 10 washings diagnosed as negative for high-grade TCC, low-grade TCC cannot be ruled out, the final diagnoses were low-grade TCC in 9 and high-grade TCC in 1. The cytologic features seen most commonly in association with low-grade TCC are listed in Table 1. These include the presence of more than 5 papillary groups per slide (100%), cellular overlapping or crowding as illustrated in **Image 3** (89%), and nuclear hyperchromasia (78%). The single washing that corresponds with a tissue diagnosis of high-grade TCC showed some features of high-grade TCC, such as more than 10 papillary groups and cellular overlapping, coarse chromatin, and nuclear hyperchromasia. However, it lacked individual tumor cells and nuclear pleomorphism, features often seen in high-grade TCC.

Of the 11 washings diagnosed as negative, the corresponding tissue showed no evidence of TCC or dysplasia in 9 and high-grade TCC in 2 (both from the same patient). Even retrospectively, these washings lacked key features of either low- or high-grade TCC.

Among the 5 unsatisfactory washings, which all were due to poor cellularity, the corresponding tissue showed high-grade TCC in 2, low-grade TCC in 1, and absence of TCC or dysplasia in 2.

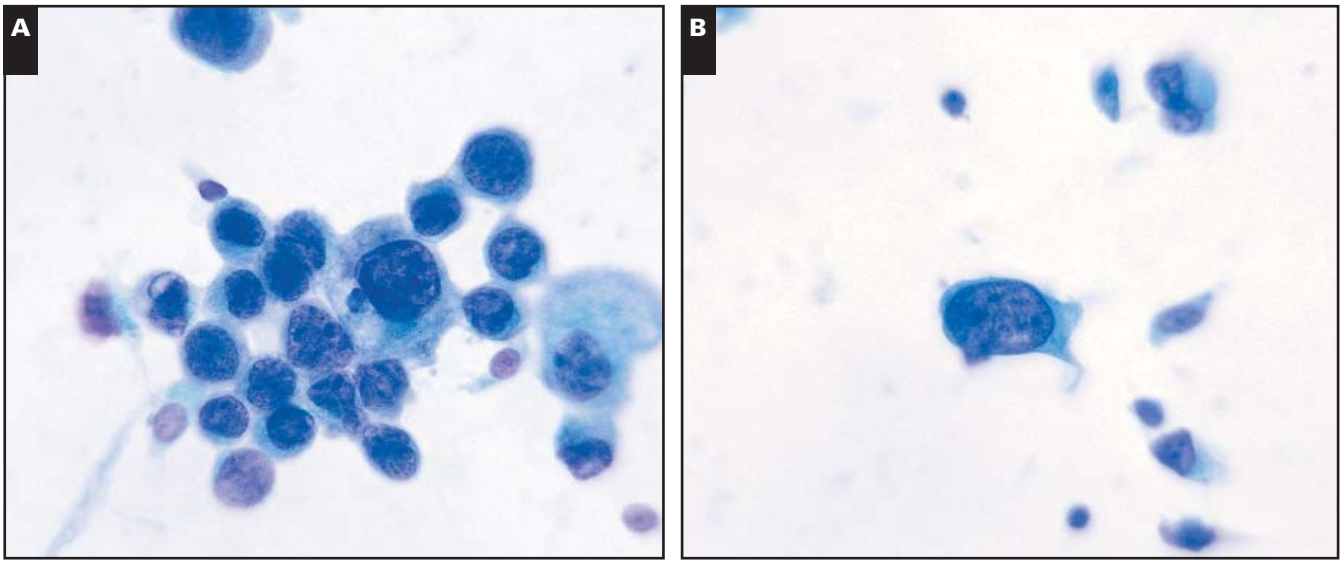

Image 1 High-grade transitional cell carcinoma. A cluster of neoplastic cells with a high nuclear/cytoplasmic ratio, nuclear hyperchromasia, and pleomorphism (**A**) and irregular nuclear membrane in an isolated cell (**B**). (Papanicolaou, ×530)

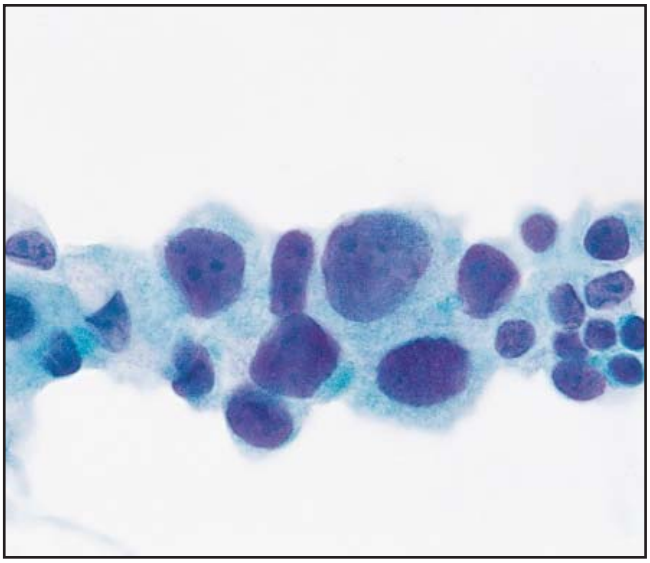

Image 2 False-positive cytologic diagnosis. A diagnosis of transitional cell carcinoma (TCC) was made on the basis of cellular overlapping, hyperchromasia, and an increased nuclear/cytoplasmic ratio in this washing. A biopsy and 2 pelvic washings performed shortly after the false-positive washing were negative. However, a washing performed 1 year later was reported as positive, and a nephroureterectomy confirmed the presence of grade II/III TCC (Papanicolaou, ×530).

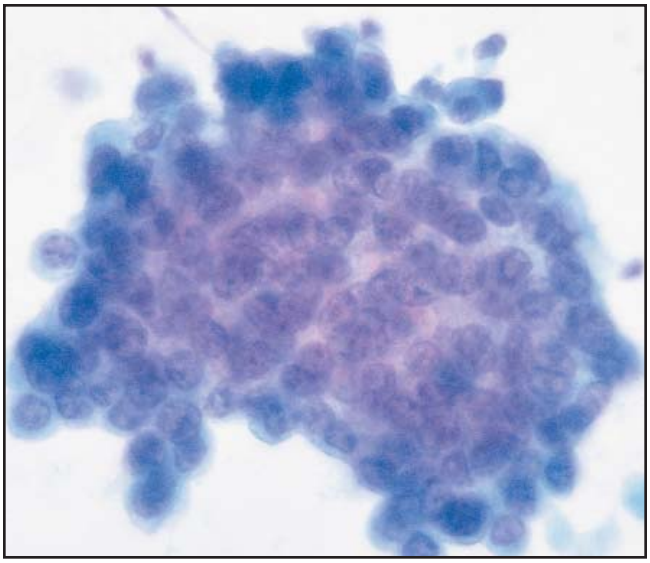

Image 3 Low-grade transitional cell carcinoma. A papilla showing cellular crowding, some separation of individual cells at the edge, and nuclear hyperchromasia (Papanicolaou, ×530).

Cases With Clinical Follow-Up

Histologic correlation was not available in 48 washing specimens obtained from 29 patients **Table 3**. The reasons for the upper urinary tract evaluation in these patients included contralateral upper urinary tract TCC, microhematuria with a workup negative for TCC of the lower urinary tract, and a filling defect in the upper urinary tract shown on retrograde pyelography. The causes of the filling defects were found to include calculi, hematoma/blood clots, and congenital tortuosity of the ureters. Low- or high-grade TCC of the renal pelvis was not identified on clinical follow-up in these cases (up to 4.5 years). In the single positive case, thorough clinical evaluation did not identify any lesion to warrant biopsy, and numerous other washings from the same side were negative. This patient, however, had a contralateral pelvic TCC.

Table 3
Cytologic Diagnoses in 48 Renal Pelvic Washings Without Tissue Correlation: Clinical Follow-up

	Cytologic Diagnosis (No. of Washings)			
Final Diagnosis (No. of Patients)	**Positive for High-Grade TCC**	**Negative for High-Grade TCC; Rule out Low-Grade TCC**	**Negative**	**Unsatisfactory**
Contralateral TCC (n = 7)	1	1	9	0
Prostate carcinoma (n = 3)	0	1	6	0
Hematuria not due to TCC (n = 4)	0	1	4	0
Renal calculus (n = 4)	0	5	0	0
Ureteral carcinoma (n = 2)	0	2	2	0
Prostate and bladder carcinoma (n = 1)	0	1	3	0
Bladder carcinoma (n = 1)	0	0	2	1
Congenital ureteral abnormality (n = 1)	0	0	1	1
No significant history (n = 1)	0	0	1	0
Record unavailable for review (n = 5)	0	1	5	0
Total (n = 29)	1	12	33	2

TCC, transitional cell carcinoma.

Table 4
Statistical Analysis of the Usefulness of Renal Pelvic Washings as a Diagnostic Tool for Transitional Cell Carcinoma*

Transitional Cell Carcinoma	Sensitivity	Specificity	False-Positive Rate	False-Negative Rate	Predictive Value	
					Positive	Negative
High-grade	89	97	10	11	93	95
Low-grade	100	78	22	0	43	100
Low- and high-grade	92	75	10	8	71	93

* Values are percentages.

Predictive Value of Washing Cytology

The cytologic diagnosis of high-grade TCC was sensitive and specific with values of 89% and 97%, respectively **Table 4**. The positive predictive value of a diagnosis of high-grade TCC was 93%. The cytologic diagnosis of low-grade TCC had a sensitivity and specificity of 100% and 78%, respectively. The positive predictive value of diagnosing low-grade TCC was only 43%, but the negative predictive value of a washing for low-grade TCC was 100%.

Discussion

TCC of the renal pelvis is a relatively uncommon tumor, which accounts for 4% to 5% of TCC of the urinary tract and 7% to 8% of renal tumors, but its incidence is, however, reportedly on the rise.[8] The diagnosis of upper urinary tract TCC is always a challenge.[17] Although Highman[1] reported a diagnostic sensitivity of 70% for upper urinary tract TCC in voided urine, the consensus is that these specimens are difficult to interpret. The cited reasons included degeneration of tumor cells that resulted from delayed passage into the urine, possible synchronous bladder TCCs, and an inherent "atypia" of urothelial cells of normal upper urinary tract compared with those from a normal urinary bladder.

Developments in endoscopic techniques enable direct visualization of upper urinary tract lesions for washing and brushing. This approach circumvents many diagnostic limitations of voided urine specimens. Yet, interpretation of these samplings remains quite challenging, chiefly because diagnostic criteria are not fully established, unlike for the urinary bladder. Accuracy is of paramount importance, since a *cytologic* diagnosis of renal pelvic TCC, increasingly considered as definitive for management purposes, usually results in nephroureterectomy. Furthermore, preoperative distinction between low- and high-grade renal pelvic TCC becomes increasingly important in view of the increasing acceptance of conservative surgical management, with renal preservation in cases of bilateral upper urinary tract TCC, solitary kidney, or renal insufficiency.[2,6]

Accurate diagnosis of high-grade renal pelvic TCC is possible with renal pelvic washings. Our findings concur with those of Bian et al,[11] who found high-grade TCC of the upper urinary tract readily diagnosed by numerous clusters and single cells showing nuclear irregularity, pleomorphism, hyperchromasia, and increased N/C ratios. These findings also are similar to those reported by Potts et al,[4] who, by logistic regression, found an increased N/C ratio, anisonucleosis, and nuclear overlap as the key cytologic criteria for diagnosing high-grade TCC of the upper urinary tract. The presence of nuclear overlapping was seen less frequently in our cases of high-grade TCC (72%), but it proved important in the diagnosis of low-grade TCC.

Clinical correlation is critical in interpretation of upper urinary tract cytology if false-positive and false-negative diagnoses are to be avoided. High cytologic grade reliably predicts a high-grade tumor, but the diagnosis of a low-grade tumor in cytologic material does not exclude a higher grade tumor in deeper, nonexfoliating areas.[1] This may be due to sampling or interpretive problems. The sampling error may be related to technical difficulties, lack of tumor cell exfoliation related to endophytic growth, extensive desmoplasia, or the presence of a high-grade tumor in deeper, nonexfoliating areas. Three false-negative diagnoses were encountered. One of these was diagnosed as "negative for high-grade TCC, low-grade TCC cannot be ruled out," and it showed abundant papillary groups (>10 per slide), nuclear overlapping, coarse nuclear hyperchromasia, and a slightly increased N/C ratio, but without individual tumor cells. A renal pelvic mass was identified, for which a biopsy showed a high-grade TCC, with better differentiation of the superficial portion of the tumor. The other 2 false-negative diagnoses were reported as "negative" and were obtained from 1 patient during a single procedure. These did not show any features of malignancy even on retrospective review. A biopsy also performed at that time revealed only hyperplastic urothelium and granulation tissue. A nephrectomy, performed 1 month later on clinical grounds, showed an invasive high-grade TCC with virtually no exophytic growth.

Overdiagnosis also is possible, but less frequent. One washing originally was diagnosed as "suggestive of high-grade

TCC" (Table 2), but 2 additional washings and a corresponding biopsy at the same time showed no malignancy. One year later, the patient had another "suspicious" washing result, followed by biopsy, which showed high-grade TCC. It cannot be determined whether the first washing was a genuine example of false positivity or whether the 2 corresponding negative washings and the negative biopsy represent sampling errors.

Low-grade TCC of both the urinary bladder and the upper urinary tract usually raises diagnostic dilemmas in cytopathology. Urine samples, especially those obtained from the urinary tract by endoscopy, are known to display many features that may simulate low-grade TCC. These changes include increased numbers of papillary groups of cells and mild nuclear pleomorphism with nuclear crowding. Data from the present study show that although a definite cytologic diagnosis of low-grade TCC is problematic, many findings may at least suggest this possibility. Among 10 tissue-confirmed low-grade TCCs, low-grade TCC was suggested cytologically in 9 with the diagnosis "negative for high-grade TCC; low-grade TCC cannot be ruled out," whereas the washing of the remaining case was unsatisfactory.

Subtle cytologic clues have been proposed to overcome the diagnostic problem with variable success. Kannan et al[18] suggested that the ragged borders of the papillary groups are more compatible with low-grade TCC. The cellular features most suggestive of low-grade TCC, in our experience, are more than 5 papillary groups per cytocentrifuged slide (seen in all cases of low grade TCC), cellular overlapping, and nuclear hyperchromasia. Bian et al[11] also identified 3-dimensional clusters as a feature of a low-grade TCC. These criteria are sensitive, but may not be specific for low-grade TCC. For example, although 5 washings from 4 patients were classified as "negative for high-grade TCC; low-grade TCC cannot be ruled out," based partially on the abundance of papillary groups, clinical follow-up revealed renal calculi in all of them. It has been shown that renal pelvic lithiasis is one of the most important causes of a false-positive diagnosis of low-grade TCC, at a rate of 4% to 7%.[1] Other cytologic features studied were not helpful for a definitive diagnosis of low-grade TCC (Table 3). The presence of superficial umbrella cells within a washing was not helpful for excluding a low-grade TCC, as pelvic washings from 67% of low-grade TCCs in the present study contained these cells. Clusters of low-grade neoplastic cells devoid of umbrella cells may be seen together with many groups of benign cells in which umbrella cells are identified. The positive predictive value of suggesting low-grade TCC is only 43%, but the negative predictive value of a washing evaluated for low-grade TCC is 100%.

Renal pelvic washings can be used to accurately diagnose high-grade TCC of the renal pelvis. Attention to key cytologic features can distinguish high-grade TCC from low-grade TCC. The diagnosis of low-grade TCC continues to be challenging. However, subtle cytologic patterns can help differentiate negative specimens from those that may represent low-grade neoplasms. The high frequency of unsatisfactory specimens (9.6%), false-positive diagnoses (10%), and false-negative diagnoses (8%) in the present study highlights the continued difficulty in sampling and diagnosing upper urinary tract TCCs, even with the advent of new endoscopic techniques and improved histologic and cytologic criteria.

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