Accuracy of Urine Cytology and the Significance of an Atypical Category

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Key Words: Urine; Cytology; Atypia; High grade; Follow-up

Abstract

The “atypical urothelial cell” cytologic category is nonstandardized. We subclassify atypical cases to “atypical, favor a reactive process” or “atypical, unclear if reactive or neoplastic.” We evaluated the predictive significance of atypical cases by looking at their histologic follow-up. Among the 1,114 patients and 3,261 specimens included, 282 specimens had histologic follow-up. An atypical diagnosis did not carry a significant increased risk of urothelial neoplasia compared with the benign category. Although an “atypical unclear” diagnosis carried a higher rate of detection of high-grade cancer on follow-up biopsy in comparison with “atypical reactive” or “negative” diagnoses (26/58 [45%] vs 15/52 [29%] and 16/103 [15.5%], respectively), this difference was not statistically significant. These results suggest that dividing atypical cases into 2 categories based on the level of cytologic suspicion of cancer does not add clinically relevant information within the atypical category. They also raise the question of the significance of the atypical category altogether.

Urine cytology is an essential modality for the detection of urothelial neoplasia. It has various indications that generally fall in 2 principal groups: in the evaluation of patients with genitourinary symptoms, especially hematuria, and as a surveillance tool for patients with a history of bladder cancer.

The accuracy of urine cytology depends on several factors that are mainly related to tumor grade, the nature of specimen, and sampling. It has long been known that urine cytology is accurate in the diagnosis of high-grade urothelial carcinoma (HGUCA) with cytohistologic correlation reported as high as 98%.1 In contrast, it carries a much lower diagnostic yield for low-grade urothelial neoplastic lesions that include papillary neoplasm of low malignant potential (PUNLMP) and low-grade papillary urothelial carcinoma (LGUCA), with sensitivity and specificity values as low as 8.5% and 50%, respectively.2 Moreover, the specimen type also seems to impact the predictive value of urine cytology, with voided specimens being more specific and slightly less sensitive than instrumented specimens in 1 study.2 This higher degree of specificity could be explained in part by the absence of the instrumentation-induced reactive changes with the resulting cell clustering, making the interpretation of the cytologic findings in voided urine more straightforward. Finally, several studies have shown that the number of samples increases the sensitivity of urine cytology, especially in the detection of high-grade lesions.3-6

Despite the fact that the usefulness of urine cytology was described more than 60 years ago by Papanicolaou and Marshall,7 a major limitation of urine cytology, in contrast with the Bethesda System for reporting cervicovaginal cytology, is the lack of consensus regarding the terminology and
diagnostic criteria that should be used for urothelial atypia. Indeed, whereas the reactive and HGUCa categories generally cause few interpretation difficulties, the “atypical” category remains a wastebasket that encompasses different processes (eg, cell clusters, poorly preserved cells, quantitatively low number of cytologically atypical cells) and is used variably by individual cytopathologists in different institutions.

In an attempt to standardize the diagnostic categories for urine cytology, the Papanicolaou Society of Cytopathology recommended in 2004 a diagnostic scheme that included an “atypical urothelial cells” category. The Society also suggested that a comment be included in the cytology report to further classify the atypia as reactive or neoplastic. However, the criteria that should be used to separate reactive atypia from neoplastic atypia are not clearly defined in that article nor in the literature in general.

For the last 14 years at McGill University Health Center, Montreal, Canada, we have used diagnostic terminology for urine cytology that includes an atypical urothelial category, representing a gray zone between the benign category (including reactive and instrumentation changes) and the “suspicious” and malignant categories. Our atypical urothelial category is further subclassified as “atypical, favor a reactive process” (atypical, reactive) and as “atypical, unclear if reactive or neoplastic” (atypical, unclear). Conceptually akin to the Bethesda classification for the atypical squamous cells (ASC), our institutional subclassification of the atypical category was meant to reflect the level of suspicion of the cytopathologist for the likelihood of urothelial neoplasia and to, hopefully, help guide clinicians in their choice of follow-up for patients.

In a nutshell, the atypical, favor reactive category was meant to convey a low probability of malignancy for which only conservative follow-up was intended, whereas the atypical, unclear category was more conceptually akin to the “ASC, cannot rule out high-grade lesion (ASC-H)” and was meant to alert clinicians to take a more aggressive investigative stance. Despite the efforts by cytopathologists in subclassifying the atypical urothelial category, the clinicians and urologists at our institution often do not react differently to this subclassification, usually considering the atypical category equivalent to a negative result as long as the cystoscopy and upper tract imaging results are normal. This discrepancy reflects the different interpretation that clinicians and pathologists have of an atypical diagnosis. Indeed, many studies conducted on urine cytology allude to this fact by considering atypical cases as negative in their analyses.

Therefore, this study aimed to evaluate the diagnostic yield of urine cytology in daily practice with a specific emphasis on the evaluation of the atypical urothelial category with the histologic follow-up of its 2 subcategories at McGill University Health Center.

Materials and Methods

Case Selection

From the laboratory information system, we retrieved all the cytologic urine specimens examined from January 1 to July 1, 2006. Based on the retrieved list of patients, we then searched for all the subsequent cytologic and surgical specimen reports available up to June 2008 to ensure a minimum of 2 years’ follow-up. The following clinical and pathologic parameters were captured: date of collection, clinical history (surveillance for urothelial carcinoma, evaluation of genitourinary symptoms such as hematuria or urinary retention, postrenal transplantation surveillance, urine eosinophilia evaluation), and type of specimen (voided, washing, or catheterized).

Cytology

While the voided urine specimens were all prepared as ThinPrep slides (Hologic, Marlborough, MA), all other types of urine specimens were prepared by conventional methods such as Cytospin (Shandon, Pittsburgh, PA) or smear preparation following centrifugation. All slides were stained with the Papanicolaou stain. This study was designed to reflect a real-life practice setting rather than being an academic exercise to assess various cytomorphologic parameters; therefore, the cytologic diagnoses used for the study were the original ones, and no slides were retrospectively reviewed. A similar approach has been used by others.

The cytologic classification included the following categories: benign (including reactive urothelial cells and instrumentation effects); atypical, favor reactive; atypical, unclear if reactive or neoplastic; suspicious for urothelial carcinoma; and urothelial carcinoma. It should be noted that all cases had been signed out by 1 of 4 pathologists with subspecialty training in cytopathology; all were familiar with our institutional criteria used for subclassifying the atypical urothelial category into the atypical, favor reactive vs the atypical, unclear category. In summary, we generally consider the urothelial cells in voided specimens as atypical when they exhibit a nuclear/cytoplasmic (N/C) ratio exceeding 50%. The atypical, reactive category is reserved for the atypical cases, in which the cells are in cell clusters and have bubbly cytoplasm with intact and smooth nuclear membranes, often with a conspicuous nucleolus. The criteria used to make an atypical, reactive diagnosis are based on some morphologic studies suggesting that cell clusters in voided specimens are associated with higher rates of cancer on histologic follow-up. However, we restrict this diagnosis to clusters displaying a high N/C ratio (>50%).

On the other hand, the atypical, unclear category is generally used when the urothelial cells, even if single or few, appear to be degenerated but display a high N/C ratio, intact and irregular nuclear membranes with clumpy chromatin, and/
or a dark India ink chromatin pattern Image 2. The majority of cells diagnosed as atypical, unclear are morphologically similar to the cells that have been termed pseudodegenerated cells by Renshaw.13 These cells with irregular nuclear membranes have been reported by numerous authors to be associated with high-grade urothelial carcinoma, but they are too degenerated (or pseudodegenerated) to reach a diagnosis of suspicious or positive for malignant cells.14-16 In general, in instrumented specimens, our threshold for using the atypical category goes up and requires more nuclear atypia than in voided urine specimens.

The histologic diagnoses used for the study were the original ones; no slides were reviewed. The histologic categories were those of the World Health Organization classification system17 and were coded as benign, urothelial papilloma, PUNLMP, LGUCA, HGUCA, and urothelial carcinoma in situ (CIS).

Cytologic-Histologic Correlation: General Approach

For the cytologic-histologic follow-up and correlation, histology was considered the “gold standard,” acknowledging the fact that this would create a certain bias owing to the possibility of sampling error, even in biopsy. In fact, a positive cytologic result in the presence of a negative biopsy result is not always indicative of a false-positive cytologic result. Theoretically, cytology allows sampling of the entire urologic tract, including the upper urinary tract (renal pelvis and ureters), which is not appreciated at the time of cystoscopy.

This contrasts with the limited but more targeted sampling of a biopsy. This being said, owing to the absence of long follow-up period in our cohort of patients, biopsy result was the only end point variable with which cytology could be correlated. In addition, and to avoid erroneous correlation, we selected an arbitrary period of 1 year as the maximal interval allowed between cytology and histology to assess concordance. The same approach was used in previous studies1 and was thought to be clinically valid for the urologists in our institution. A longer interval, such as 3 years, might, in our opinion, allow new tumors to be part of the follow-up, that is, tumors that were not present when the index cytologic specimen was taken.

All patients who underwent a biopsy also had a cytologic specimen submitted at the time of biopsy or in a very short time preceding the biopsy (<2 months). Of note, when signing out cytologic specimens that are obtained at the same time that a biopsy is performed, the biopsy results are not known by the cytopathologist, mainly for 2 reasons: (1) the fast turnaround time of cytologic cases in comparison with surgical cases and (2) our practice in which cytologic results are provided regardless of the histologic findings (except on very rare occasions).

The histology was considered positive when any of the following diagnoses was made: PUNLMP, LGUCA, and HGUCA. Because of the different atypical categories in our data, we used 3 cytologic thresholds to consider a cytologic diagnosis as positive Table 1: (1) Any atypical diagnosis
was considered negative, therefore limiting positive cytology to cases that were categorized as suspicious for or positive for urothelial carcinoma (threshold 1). This threshold appears to be the closest to the urologists' current approach and daily practice. (2) The atypical, unclear category was included as positive cytology (threshold 2). (3) Any atypical cytologic results, including the atypical, reactive cases, were considered positive (threshold 3).

The cytologic-histologic follow-up and correlations were classified as concordance (when the cytologic and histologic results were negative or positive) or as discordance (when one of the two results was positive and the other negative). Arbitrarily, cytologic-histologic follow-up and correlation was defined as the correlation between cytologic cases and their immediate following corresponding biopsy. Therefore, when a patient had more than one biopsy separated by cytologic specimens, the number of follow-ups and correlations was equal to the number of biopsies. When more than one cytologic specimen existed in a cytohistologic follow-up and correlation, the worst was used as representative of the group for the cytologic-histologic correlation as long as it was rendered within 1 year of the follow-up biopsy [Table 2].

**Statistical Analysis**

We calculated the overall sensitivity and specificity of urine cytology and then compared its yield for low-grade (PUNLMP and LGUCA) and high-grade lesions (HGUCA and CIS). We also separately measured the performance of cytology in the following: (1) surveillance of patients with a history of urothelial cancer in comparison with primary detection of cancer in patients with urologic symptoms and (2) voided specimens in comparison with instrumented specimens. Correlation between cytologic diagnoses and histologic follow-up was conducted using multivariate logistic regression analysis and the \( \chi^2 \) test using Minitab, version 14.11 (State College, PA).

## Results

### Specimen Type

Included in the study were the data for 1,114 patients corresponding to 3,261 specimens (2,979 cytologic and 282 histologic specimens). The types of cytologic specimens were as follows: 2,281 voided urine, 415 cystoscopy-induced urine, 156 catheterized urine, 101 bladder washes, 20 ureteral washes, 1 ureteral brush, and 5 ileal conduit specimens. The voided/instrumented specimen ratio was 3.27:1.

### Clinical Manifestations

The majority of patients were under surveillance following a diagnosis of urothelial neoplasia (663 [48.2% of cases]); 22.3% of cases (n = 293) were seen for the evaluation of hematuria, while the evaluation of other lower genitourinary tract symptoms was the clinical setting in 10.9% of cases (n = 143: urinary tract infection, 46; urgency, 5; bladder stones, 6; urinary retention, 45; incontinence, 12; frequency, 27; and benign prostatic hyperplasia, 2). A small percentage of cases had miscellaneous symptoms stated in the requisition (bladder tumor, 3; abdominal pain, 74; cystocele, 1; urine eosinophils evaluation, 1; kidney mass, 2; lymphoma, 1; renal transplantation, 39; ureteral tumor, 3; urethral stricture, 13; vesicoureteral stenosis, 1; abdominal mass, 1; and hereditary nonpolyposis colorectal cancer, 1). In 10.4% of cases no clinical history was provided.

### Cytologic Diagnoses

Overall, the atypical category constituted 23.2% of all urine cytologic cases. Of those cases, 59.3% (410/691) and 40.7% (281/691) belonged to the atypical, reactive and the atypical, unclear categories, respectively. An atypical diagnosis was more commonly used in voided specimens (25.9%) or in a surveillance setting (26.5%) than in instrumented specimens (15.0%) or in the evaluation of patients for genitourinary symptoms (18.7%). In comparison, a malignant diagnosis (5.5% of cases) was more often rendered in instrumented specimens (10.3%) or in a surveillance setting (7.7%). Complete results are shown in [Table 3](#).
Cytologic-Histologic Correlation

The study included the data for 199 patients corresponding to 282 cytologic-histologic follow-ups and correlations (608 cytologic and 282 biopsy specimens) were included. The vast majority of cytologic-histologic follow-ups and correlations (263/282 [93.3%]) were found to be confined to a period that was less than 6 months between the worst cytologic diagnosis and the subsequent biopsy finding; in fact, the mean intervening time between cytologic and histologic diagnoses was 51 days.

The voided/instrumented specimen ratio was 2:1 (405 voided, 104 cystoscopy urine, 51 catheterized urine, 34 bladder washes, and 14 ureteral washings). Whereas 91.8% of biopsies (259/282) were performed in a surveillance setting following a positive cytologic or an abnormal cystoscopic examination, only 7.4% (21/282) were performed in the evaluation of genitourinary symptoms. One patient had a history of renal cell carcinoma, and 4 had unknown clinical histories.

On histologic follow-up, an atypical, reactive diagnosis had an overall predictive value for a bladder neoplasm similar to that of an atypical, unclear diagnosis (77% and 79%, respectively); however, the distribution of the types of urothelial neoplasia was different between the 2 atypical categories. While the majority of positive cases that were called atypical, unclear on cytology turned out to be high-grade lesions (HGUCA and CIS) on biopsy (57% [26/46] high and 43% [20/46] low grade), the majority of positive cases in the atypical, reactive category were low-grade lesions (ie, 63% [25/40] low-grade vs 38% [15/40] high-grade lesions) Table 4. However, logistic regression analysis of the histologic outcome of tumor (low or high grade) demonstrated that in a multivariate model, neither an atypical, reactive nor an atypical, unclear diagnosis was significantly related to presence of urothelial neoplasm on follow-up biopsy. Nevertheless, cytologic suspicion for or a diagnosis of high-grade carcinoma was strongly related to histologic outcome (P = .005). The same results were obtained when cytologic diagnoses were correlated with only the presence of high-grade carcinoma on histology as a positive outcome Table 5. These findings are further illustrated in the receiver operating characteristic plot in Figure 1. The plot demonstrates that cut points in cytologic diagnoses of greater than negative and greater than atypical, reactive yield sensitivities and specificities such that their points fall close to the line of nondiagnostic results. On the other hand, a cytologic cut point of greater than atypical, unclear (ie, presence of or suspicion for high-grade carcinoma cells) yields a point far from the line of nondiagnostic results.

Table 4

<table>
<thead>
<tr>
<th>Histologic Outcome</th>
<th>Cytologic Category</th>
<th>P for Any Tumor</th>
<th>P for High-Grade Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical, reactive</td>
<td>.996</td>
<td>.115</td>
<td></td>
</tr>
<tr>
<td>Atypical, unclear</td>
<td>.620</td>
<td>.432</td>
<td></td>
</tr>
<tr>
<td>“Suspicious” for UCA/UCA</td>
<td>.005</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

UCA, urothelial carcinoma.

Table 5

Logistic Regression Analysis of Categories of Urine Cytology vs Two Histologic Outcomes: The Presence of UCA (Low and High Grade) or High-Grade Carcinoma

Table 3

<table>
<thead>
<tr>
<th>Specimen/Clinical Setting</th>
<th>Overall (n = 2,979)</th>
<th>Voided (n = 2,281)</th>
<th>Instrumented (n = 698)</th>
<th>Surveillance (n = 1,808)</th>
<th>New Symptoms (n = 827)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>2,123 (71.3)</td>
<td>1,593 (69.8)</td>
<td>521 (74.6)</td>
<td>1,189 (65.8)</td>
<td>648 (78.4)</td>
</tr>
<tr>
<td>Atypical, reactive</td>
<td>410 (13.8)</td>
<td>357 (15.7)</td>
<td>56 (8.0)</td>
<td>270 (14.9)</td>
<td>98 (11.9)</td>
</tr>
<tr>
<td>Atypical, unclear</td>
<td>281 (9.4)</td>
<td>234 (10.3)</td>
<td>49 (7.0)</td>
<td>209 (11.6)</td>
<td>57 (6.9)</td>
</tr>
<tr>
<td>“Suspicious” for UCA/UCA</td>
<td>165 (5.5)</td>
<td>97 (4.3)</td>
<td>72 (10.3)</td>
<td>140 (7.7)</td>
<td>24 (2.9)</td>
</tr>
</tbody>
</table>

UCA, urothelial carcinoma.

* Data are given as number (percentage).

Table 4

Cytologic-Histologic Correlation by Diagnostic Categories

Table 5

CIS, carcinoma in situ; HGUCA, high-grade UCA; LGUCA, low-grade UCA; PUNLMP, papillary urothelial neoplasm of low malignant potential; UCA, urothelial carcinoma.

* Data are given as number (percentage).
By considering any atypical cytologic diagnosis as negative, the sensitivity and specificity values of urine cytology for urothelial neoplasia were 29.6% and 85%, respectively. As expected, low-grade lesions were often missed on urine cytology, in contrast with high-grade lesions (sensitivity values of 8.1% and 46.3%, respectively). On the other hand, the specificity of cytology for low- and high-grade lesions was equal (85%).

Changing the threshold to considering the atypical, unclear category among the positive results significantly increased the sensitivity of cytology for high-grade lesions (sensitivity, 70.3%; \( P = .0001 \)), albeit with a smaller but still significant decrease in specificity (specificity, 66.6%; \( P = .015 \)).

Considering any atypical diagnosis as positive resulted in a significantly lower degree of specificity for high- and low-grade lesions (48.4% and 49.2%, respectively).

In general, the specificity was lower for low- and high-grade lesions in voided specimens or in a follow-up setting, and this was true regardless of the considered threshold of a positive cytologic diagnosis. On the other hand, the sensitivity for low-grade lesions was higher in voided specimens in contrast with high grade lesions, which were detected more often on instrumented specimens. Complete results are shown in Table 6.

### Diagnostic Yield, Sensitivity, and Specificity

By considering any atypical cytologic diagnosis as negative, the sensitivity and specificity values of urine cytology for urothelial neoplasia were 29.6% and 85%, respectively. As expected, low-grade lesions were often missed on urine cytology, in contrast with high-grade lesions (sensitivity values of 8.1% and 46.3%, respectively). On the other hand, the specificity of cytology for low- and high-grade lesions was equal (85%).

### Discussion

Many studies have evaluated the accuracy of urine cytology in the detection of bladder cancer. Overall, the reported sensitivity ranges from 20% to 97.3%; specificity ranges from 74% to 99.5%. In comparison, the ranges of sensitivity and specificity in our study were 29.6% to 69.0% and 49.2% to 85.0%, respectively, depending on which threshold was used to consider a cytologic result positive. These numbers, which are somewhat low compared with those reported in the literature, have to be interpreted after taking into account several factors.

### Table 6

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any atypical diagnosis considered negative</td>
<td>29.6</td>
<td>85.0</td>
<td>8.1</td>
<td>85.0</td>
<td>46.3</td>
<td>85.0</td>
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<tr>
<td>Voided</td>
<td>23.0</td>
<td>81.8</td>
<td>8.2</td>
<td>85.7</td>
<td>44.2</td>
<td>82.0</td>
</tr>
<tr>
<td>Instrumented</td>
<td>31.8</td>
<td>90.3</td>
<td>5.4</td>
<td>90.0</td>
<td>51.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Follow-up</td>
<td>28.1</td>
<td>82.1</td>
<td>7.6</td>
<td>82.1</td>
<td>51.2</td>
<td>81.8</td>
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<tr>
<td>New symptoms</td>
<td>25.0</td>
<td>100.0</td>
<td>11.0</td>
<td>100.0</td>
<td>34.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Atypical, unclear diagnosis considered positive</td>
<td>50.5</td>
<td>80.6</td>
<td>27.3</td>
<td>67.2</td>
<td>70.3</td>
<td>66.6</td>
</tr>
<tr>
<td>Voided</td>
<td>45.0</td>
<td>59.0</td>
<td>28.2</td>
<td>62.0</td>
<td>68.8</td>
<td>59.0</td>
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<tr>
<td>Instrumented</td>
<td>48.8</td>
<td>80.6</td>
<td>19.0</td>
<td>80.6</td>
<td>70.5</td>
<td>80.0</td>
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<td>Follow-up</td>
<td>47.1</td>
<td>64.2</td>
<td>28.2</td>
<td>64.2</td>
<td>68.2</td>
<td>63.6</td>
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<tr>
<td>New symptoms</td>
<td>55.0</td>
<td>81.8</td>
<td>22.0</td>
<td>81.8</td>
<td>82.6</td>
<td>82.0</td>
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<tr>
<td>Any atypical diagnosis considered positive</td>
<td>69.0</td>
<td>49.2</td>
<td>50.0</td>
<td>49.2</td>
<td>85.0</td>
<td>48.4</td>
</tr>
<tr>
<td>Voided</td>
<td>66.6</td>
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<td>56.4</td>
<td>45.4</td>
<td>82.0</td>
<td>45.4</td>
</tr>
<tr>
<td>Instrumented</td>
<td>59.0</td>
<td>61.2</td>
<td>24.3</td>
<td>61.0</td>
<td>84.3</td>
<td>60.0</td>
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<tr>
<td>Follow-up</td>
<td>68.3</td>
<td>46.4</td>
<td>53.2</td>
<td>46.4</td>
<td>85.3</td>
<td>45.4</td>
</tr>
<tr>
<td>New symptoms</td>
<td>62.5</td>
<td>63.6</td>
<td>33.3</td>
<td>63.6</td>
<td>87.0</td>
<td>63.6</td>
</tr>
</tbody>
</table>

CIS, carcinoma in situ; HGUCA, high-grade UCA; LGUCA, low-grade UCA; PUNLMP, papillary urothelial neoplasm of low malignant potential; UCA, urothelial carcinoma.
The first important point worth considering when reading the literature related to urine cytology is the definition of what constitutes a positive cytologic result. The vast majority of studies considered any atypical cytologic diagnosis as negative and reserved the term positive for cases that were positive for urothelial carcinoma or suspicious for urothelial carcinoma. However, the criteria used to define an atypical or suspicious for urothelial carcinoma diagnosis are seldom discussed in individual studies. Therefore, one might correctly assume that the lack of uniform terminology and diagnostic criteria in urine cytology makes the comparison between different studies dealing with the subject somewhat arbitrary.

In only 1 previous study by Raab et al., the authors addressed this issue and calculated the efficacy of cytology by using 2 different definitions of a positive cytologic diagnosis: first, by considering any atypical diagnosis as negative and second, by considering any atypical diagnosis as positive. It is interesting that when the atypical urine cytologic result was considered negative, the sensitivity and specificity of cytology for high-grade lesions in the study by Raab et al. were comparable to our results with slightly lower sensitivity rates in the present study, probably owing to the high number of low-grade lesions in our cohort of patients (sensitivity values for voided and instrumented specimens of 49.2% and 65%, respectively, in the study by Raab et al. compared with 44.2% and 51% in our study, and specificity of 89% and 85.7% in the study by Raab et al. compared to 82% and 90% in our study, respectively). On the other hand, comparing the sensitivity and specificity of cytology for high-grade lesions in the 2 studies yielded mixed results because Raab et al. used 2 thresholds for a positive cytologic diagnosis instead of 3, as in ours. Nevertheless, the 74.6% and 90% sensitivity rates and 66.2% and 61.9% specificity rates for voided and instrumented specimens reported by Raab et al. were close to our rates using threshold 2 in some regards and threshold 3 in others (Table 6).

Second, some of the cytohistologic studies that validated the accuracy of urine cytology were conducted retrospectively, with cases being reviewed by experts in the field after the original diagnoses were rendered; therefore, the high rates of sensitivity of cytology for high-grade lesions that are quoted in the literature might not be entirely reflective of real-life practice. In contrast, in our study, we used the cytologic diagnoses that had been originally determined, reflecting a real-life situation.

Third, the relatively low specificity in our study comes from the fact that sensitivity and specificity were calculated based on the number of cytologic-histologic follow-ups and correlations (or biopsies) rather than the number of patients. Among the 9 patients who had a false-positive result for HGUCA/CIS on cytology, only 4 had a repeated biopsy, and among the 4, 3 were diagnosed with a high-grade lesion within the following year. Therefore, the specificity of cytology for high-grade lesions in our series is, in reality, higher than 85% but was calculated as such for study design purposes.

Fourth, the low sensitivity of urine cytology for low-grade lesions (range, 0%-50%)[2,20] and the fact that these slow-growing and rarely invasive tumors, even if missed initially, would subsequently be detected by cystoscopy or biopsy without significant tumor progression make urine cytology mainly an important tool to detect high-grade lesions. In that regard, our series comprised a high number of low-grade lesions on histologic follow-up (110/218 [50.5%]), which shifted our results toward the low end of the reported spectrum when calculating the overall performance of urine cytology. In comparison, the yield of cytology in our study was significantly higher for the detection of high-grade lesions (sensitivity and specificity as high as 85%).

Finally, in this type of cytohistologic correlative studies, the interval between cytology and subsequent biopsy has a major confounding role in determining the accuracy of cytology. The longer the interval between cytology and histology, the more discrepancies between the 2 results one would expect to see because the initial cytologic result might not be reflective of the urothelial tract pathologic state at time of biopsy. One might correctly assume that the maximum 1-year interval between cytologic and biopsy results that was allowed in this study could have affected the reported cytologic sensitivity and specificity rates. However, in our study, 93.3% of follow-up biopsies of cytologic specimens (ie, the worst cytologic diagnosis) were obtained less than 6 months preceding the biopsy with a mean interval of 51 days. Therefore, in view of this relatively short interval between cytology and histology in the vast majority of our cases, discordance between the 2 was less likely to be due to a new disease process at the time of biopsy.

The main objective of our study was to evaluate the rate and significance of an atypical cytologic diagnosis. The atypia rate in the literature ranges from 1.9% to 20.1%.[2,10,21] In comparison, the atypical category constituted 23.2% of all cases in our series. Because the atypical urothelial category is poorly defined in the literature, interpretation of the comparative data between studies is very difficult. Indeed, unlike the ASC in the Bethesda System for which the diagnostic criteria are well defined and for which guidelines exist for the proportion of cases that should fall into that category in a laboratory, the atypical urothelial category is poorly defined, and no such guidelines exist.

Renshaw[13] attempted subclassifying the atypical category by using several morphologic criteria that include cellular preservation, cellular clustering, degree of atypia, and extent of atypia. In an attempt to shift the atypical category
from one that is usually ignored by urologists to a clinically meaningful one, Renshaw’s main objective was to exclude cases that did not carry clinical significance but that were still generally labeled as atypical. In our institution, the criteria used to render the majority of the atypical, unclear diagnoses are very similar to the criteria for cells termed by Renshaw as pseudodegenerated cells. These cells display India ink–type nuclei were described in the past as coy cells and were reported to carry an increased risk of high-grade urothelial carcinoma.13-16,22

The results of our study show that an atypical urothelial cell diagnosis does not have a significantly increased risk of urothelial neoplasia compared with the benign diagnostic category (Table 5 and Figure 1). The results also show that despite the fact that an atypical unclear diagnosis has a higher rate of detection of high-grade cancer on follow-up biopsy in comparison with an atypical reactive or a negative diagnosis (45% vs 29% and 15.5%, respectively), this difference remains statistically insignificant in logistic regression analysis. Therefore, it seems that dividing the atypical category into 2 categories based on the level of cytologic suspicion for cancer does not add clinically significant information within the atypical category. Moreover, these results actually question the value of the atypical diagnostic category altogether. Despite the fact that the maximum interval allowed between cytology and histology to calculate the correlation between the 2 was only 1 year in this study, this follow-up time was sufficient to demonstrate the lack of importance of the atypical categories examined. Were these categories important, we believe that their P values in Table 5 would have been at least borderline (ie, closer to .05).

Other than the relatively small number of cases included in this study, the main limitation in reaching definite conclusions based on these current data is the fact that the vast majority of cytologic specimens did not have a follow-up biopsy. Only the patients with abnormal cystoscopical findings or a cytologic result of suspicious or positive for carcinoma usually undergo such a procedure. Therefore, the correlation between cytology and histology in this context is extremely biased by the clinical impression. An accurate measurement of the significance of an atypical in comparison with a negative urine cytologic diagnosis would be possible in only 2 settings: having a histologic follow-up for all urine cytologic specimens, which is an unrealistic and scientifically unfounded approach, or having a long follow-up period without evidence of bladder cancer (ideally, >3 years) in the study population. Using the second approach would enable us to include the patients in the same group of patients having negative histologic results and would probably shed light on the real significance of an atypical urine cytologic diagnosis in comparison with negative and malignant cytologic diagnoses. A future direction will be to study the same cohort of patients included in the current series in 2 years and compare the results of both studies. However, until that time, the current available evidence from our data seems to justify the conservative stance taken by urologists when dealing with an atypical urine cytologic diagnosis.

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