Urine Cytology: A Review

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ABSTRACT

Urine cytology is being studied since many years. This simple and cost effective test can help in diagnosis of urothelial malignancies. It has undergone a series of modifications in accordance with changes in histopathological classifications. Various systems for reporting urine cytology were being followed. But still there were difficulties and confusion in patient management. As such there were no clear cut criteria which led to lack of interobserver reproducibility. With the upcoming of The Paris System of reporting urine cytology, many of the doubts cleared. This system mentions addresses the problem of sample adequacy and clearly mentions the criteria for the various categories. To top it up, it also gives clear cut guidelines for the management of each of the categories. This review gives a glimpse of the various reporting systems with special emphasis on The Paris System of urine cytology.

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Introduction

The 'matula' ,a flask for inspection of urine used by physicians of the Middle ages is even to this day depicted in the official emblems of the American Urological Association, the German Society for Urology and the Professional Association of German Urologists. [1]

Bladder cancer can be diagnosed by cystoscopic evaluation and biopsy, urine cytology and urinary biomarkers. Urine cytology is simple, cost effective and non invasive test. The presence of neoplastic cells in urine was described by Sanders in as early as 1864.[2]

However urinary oncocytology gained popularity with the publication by Papanicolaou and Marshall in 1945.[3] Bladder cancer is the most common cancer of the urinary tract and the 9th most common cancer overall.[4] There are about 74000 new cases of bladder cancer diagnosed for 2015 as per the American Cancer Society Estimate and also about 16000 deaths from bladder cancer.[5]

Discussion

Types of urine samples

Voided urine sample is the most common type of sample sent for cytological analysis. The first morning sample is avoided due to the degenerating effects produced by overnight stagnation of urine. The second morning sample is preferred. Voided urine samples the entire urinary tract from the pelvis to urethra which is referred to as the "funnel effect". But the disadvantage is the contamination by squamous cells especially in the females.[6]

Other type of sample is the catheterized urine sample which is more cellular than voided urine and lacks the contamination by squamous cells. Wash and brush samples from the bladder, ureter or pelvis can be done along with cystoscopy. These provide better cellularity , targeted sampling and lack of contamination. Other less common samples include ileal conduit and neobladder samples.

Indications for urine cytology

1. Used as a screening test for urothelial malignancies, especially in people with occupational exposure to carcinogens.
2. Used in evaluation of patients presenting with hematuria.
3. Used to monitor patients of urothelial neoplasms post treatment.
4. Used to detect infection especially of polyoma virus in patients who have undergone renal transplantation.

Processing of urine samples for cytology:

Various methods used for urine cytology include ThinPrep, AutoCytePREP, Shandon Cytospin, nitrocellulose membrane filtration and Monoprep. Most of the studies suggest that ThinPrep is the preferred method overall due to the better cytomorphologic details, cleaner background and less obscuring inflammation.[7]

The various Reporting systems for urine cytology:

The reporting systems for urine cytology went through a series of modifications in accordance with the changes in the histopathological classification of urothelial neoplasms. Lack of a uniform reporting system caused significant inter-observer variability and created a great deal of confusion to the treating surgeons.

The earliest system was proposed by G. Papanicolaou[8] way back in 1947 which included 5 classes as follows:

Class 1- Absence of abnormal or atypical cells

Class 2 - Atypical cells present but without abnormal features

Class 3- Cells with abnormal features but not sufficiently pathognomonic

Class 4- Fair number of pathognomonic cells and cell clusters

Class 5- Large number of conclusive cells and cell clusters

The positive predictive value was 94.8% for positive cytology (Class 4 or 5), 47.4% for suspicious cytology (Class 3), and 7.4% for negative cytology (Class 1 or 2) in the study published by G.Papanicolaou.[8]

With the introduction of new WHO classification of urothelial neoplasms in 1973, Professor Koss proposed a cytological classification as follows[9,10] in table 1.

TABLES: Table 1

Histology	Cytopathology
Benign	Benign urothelial cells, few ATY 1 cells
Inflammatory conditions and instrumented urine	Bland clusters/fragments; ATY 1 cells
Papilloma, grade 1 papillary carcinoma	Clusters, nuclear elongation
Grade 2 and 3 papillary carcinoma, CIS	Malignant cells; numerous ATY 2 cells

Murphy and colleagues came up with another classification[11] of thiers. They were of the opinion that low grade neoplasms cannot be differentiated from reactive processes and that a moderate rate of false positivity should be tolerated. They suggested that the term 'dysplasia' can be better used as an alternative. They reported that large cells with preserved nucleus-to-cytoplasmic ratios, smooth nuclear contours, and vacuolated cytoplasm support a benign process. The

classificationscheme proposed by Murphy et al is given below.

Classification Scheme Proposed by Murphy
Negative/reactive

Dysplastic cells

Abnormal cells, suspicious for malignancy

Malignant tumor cells

– Low-grade neoplasm
– High-grade neoplasm
– Squamous cell carcinoma
– Undifferentiated malignant tumor
– Nonepithelial neoplasm.

Later Ooms and Veldhuizen[12], in 1992 came up with another classification stating that there was lack of consensus on cytologic criteria for the term 'dysplasia' put forth by Murphy et al. This classification eliminated the term 'dysplasia'. The classification proposed by them is as follows:

Classification Scheme Proposed by E. C. Ooms
Negative cytology

Atypical cells, significance uncertain

Atypical cells, suspicious for malignancy

Neoplastic cells present

– Grade 1 carcinoma
– Grade 2 carcinoma
– Grade 3 carcinoma
– Carcinoma in-situ
– Squamous cell carcinoma
– Adenocarcinoma
– Small cell carcinoma
– Other

In 2003, then came the Papanicolaou Society of Cytopathology Task Force classification.[13] This classification included only one equivocal category –'atypical urothelial cells'. However the criteria for this equivocal category were not conclusive and they felt the need for more studies on this category. They also mentioned about the extension of ancillary studies like FISH on urine cytology specimens.

Papanicolaou Society of Cytopathology Practice Guidelines Task Force classification
I. Adequacy statement

II. General categorization
Negative for epithelial cell abnormality
Epithelial cell abnormality present (see Descriptive Diagnosis)

III. Descriptive diagnosis
Negative for epithelial cell abnormality
Infectious agents (bacterial organisms, fungal organisms, viral changes)
Nonspecific inflammatory changes
Cellular changes associated with chemotherapy or radiation
Epithelial cell abnormalities

Atypical urothelial cells (see Comments below)

Low-grade urothelial carcinoma

High-grade urothelial carcinoma

Squamous cell carcinoma

Adenocarcinoma

IV. Others
Comments section is included at the discretion of the cytopathologist.

Findings from ancillary studies can be incorporated in this section.

Then came the Diagnostic categories of the Hopkins Template for Urine Cytology Samples proposed by Owens et al[14] which is as follows:

No urothelial atypia or malignancy identified (NUAM)

Urothelial carcinoma (specify)

High-grade (HGUC)

Low-grade (LGUC)

Atypical urothelial cells of uncertain significance (AUC-US)

Atypical urothelial cells, cannot exclude HGUC (AUC-H)]

Other

But the discrepancy, the controversy and the lack of uniformity in reporting urine cytology continued. This led to a new system of reporting urine cytology which is comparable to the Bethesda system for reporting cervical cytology and thyroid cytology. This new system was put forth by a panel of international cytopathologists and urologists at the 18th International Congress of Cytology held at Paris in May, 2013. This came to be named as "The Paris System for reporting Urine Cytology".(TPS)[15]

The Paris System for reporting urinary tract Cytology:

Adequacy : Specimen is considered

> Adequate if atypical, suspicious or malignant
>
> Adequate if there is appropriate benign urothelial cellularity.
>
> Adequate if there is adequate volume in absence of appropriate benign urothelial cellularity.
>
> Inadequate if non-urothelial factors are obscuring urothelial cells.
>
> Inadequate if there is no appropriate benign urothelial cellularity in instrumented specimen.

Categories of The Paris System:

Unsatisfactory/Non diagnostic

1. Negative for High grade Urothelial Carcinoma (NHGUC)

2. This does not exclude the possibility of low grade urothelial neoplasms. These patients should be again screened in the next scheduled check-up.

3. Atypical urothelial cells(AUC)- the criteria for AUC are

   – Non-superficial and non-degenerated urothelial cells with a N:C ratio of >0.5

   – Along with one of the three below mentioned features

   – Hyperchromasia

   – Irregular coarse, clumped chromatin

   – Irregular nuclear membrane(contours)

   This category of patients should be followed up closely. In the context of previously documented urothelial neoplasm, this category should be subjected to ancillary studies like FISH, microsatellite studies, etc.

   If the N:C ratio is >0.7 along with two of the three features, then a diagnosis of "suspicious for high grade urothelial carcinoma" should be made.

4. Suspicious for High Grade Urothelial Carcinoma

   The criteria for this category include

   – N:C ratio of >0.7 and

   – Hyperchromasia

   Along with one of the two below mentioned features

   – Irregular clumped chromatin

   – Irregular nuclear contours.

   This category of patients should be followed up closely with cystoscopy, ureteroscopy and surgical biopsies.

5. High Grade Urothelial Carcinoma

   The cytological features are high cellularity, loose clusters, singles, moderate to marked pleomorphism, increased N:C ratio, irregular clumped chromatin, irregular nuclear membrane, eccentrically located large pleomorphic nuclei, prominent nucleoli, squamous/glandular differentiation,.

6. Low Grade Urothelial Neoplasm

   The features for this category are subtle and easily missed. The important feature that can be relied upon is the presence of well defined fibrovascular cores with capillaries within.

7. Other malignancies- Primary and secondary.

Conclusion

Hopefully with the upcoming of The Paris system of reporting urine cytology, there will be uniformity and good reproducibility resulting in better treatment and patient outcome.

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Competing Interests

None declared

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