Utility of Urine Cytology in Genitourinary Lesions and Implication of Paris System in the Diagnosis of Urothelial Carcinoma - Five Years of Experience from a Tertiary Care Centre at North Karnataka

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ABSTRACT

BACKGROUND

Urine cytology when combined with cystoscopy remains a gold standard in screening and surveillance of urothelial carcinoma. Paris system for reporting urine cytology (PSRUC) gives seven well defined diagnostic criteria. We aimed to analyse utility of urine cytology in patients with urogenital symptoms, compare existing institutional system (EIS) with PSRUC and assess the performance of both reporting systems in predicting subsequent high-grade urothelial carcinoma on histopathology.

METHODS

A five year retrospective study included a total of 146 urine samples from 74 patients. Each case was assigned a category according to both EIS and PSRUC system. After cyto-histological correlation, sensitivity, specificity and diagnostic accuracy of urine cytology in detecting malignancy using PSRUC and EIS were determined. Performance of urine cytology in predicting subsequent high grade urothelial carcinoma (HGUC) was assessed for both reporting systems.

RESULTS

PSRUC resulted in reduction in number of cases assigned to atypical category (10.5 % vs. 3.4 %) and increase in low grade carcinomas assigned to NGUC category (66 % vs. 100 %). Positive predictive value (PPV) for predicting subsequent high grade urothelial carcinoma for HGUC and SHGUC category remained the same (100 %). Sensitivity (66.67 % vs. 55.5 %), specificity (100 % vs. 85.71 %) and diagnostic accuracy (81 % vs. 68.75 %) was improved with application of PSRUC when compared to EIS. Two cases of genitourinary tuberculosis were diagnosed.

CONCLUSIONS

PSRUC improves predictive accuracy of subsequent high-grade urothelial carcinoma on histopathology and it ensures uniformity in reporting. Judicious use of urine cytology might aid in early diagnosis of infectious conditions like tuberculosis.

KEYWORDS

PSRUC, Urine Cytology, High Grade Urothelial Carcinoma

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BACKGROUND

Urine examination serves as a very important tool in day-to-day cytology practice. When combined with cystoscopy, it remains as a gold standard, in screening and surveillance of urothelial carcinoma.[1] Sensitivity of urine cytology depends on type of the specimen, underlying clinical condition and grade of urothelial tumour.[2] It has been proven to be highly specific and sensitive for the detection of high grade urothelial cancer though its value is limited in diagnosis of low grade urothelial tumours.[3] Most of the problems in urine cytology arises due to equivocal or atypical results, which create management ambiguities.[4]

Several existing classification systems of urine cytology lacked standard definitions, strict criteria, universal acceptance and suffered interobserver variability.[5] Paris system for reporting urinary cytology (PSRUC) proposed in the year 2013 gives seven diagnostic categories namely 1. Nondiagnostic / unsatisfactory, 2. Negative for high grade urothelial carcinoma (NHGUC), 3. Atypical urothelial cells (AUC), 4. Suspicious for high grade urothelial carcinoma (SHGUC), 5. High grade urothelial carcinoma (HGUC), 6. Low grade urothelial neoplasm (LGUN), 7. Other: Primary and secondary malignancies and miscellaneous lesions. These categories are well defined by means of stringent criteria, are associated with a known risk of malignancy and have further clinical implications. This classification advocates improving sensitivity and specificity for the diagnosis of HGUC.[6]

We aimed to analyse utility of urine cytology in patients with urogenital symptoms, compare existing institutional system (EIS) with PSRUC and to assess the performance of both reporting systems (PSRUC and EIS) in predicting subsequent high grade urothelial carcinoma on histopathology.

METHODS

A retrospective study was conducted for a period of five years between Jan 2015 to December 2019. A total of 160 urine samples were received in cytopathology laboratory from 82 patients. At least 30 ml of freshly voided or well-preserved urine sample collected from patients with urogenital symptoms was included in the study. Patients without urogenital symptoms (n = 6) and insufficient samples (n = 2) were excluded from the study. Hence, 146 samples obtained from 74 patients were included. Clinical, radiologic and cystoscopy findings were archived from medical records. Approval from institutional ethics committee was obtained.

Minimum of 20 - 30 ml of urine samples were processed using cytospin for 5 minutes at 1500 rpm (Cellspin I THARMAC). Four slides were prepared for each sample and were stained with hematoxylin and eosin, Leishman and Papanicolaou following standard procedures. Ziehl Neelsen staining was done for all cases to detect the presence of acid-fast bacilli to rule out tubercular aetiology. Cell blocks were prepared by plasma thrombin method wherever possible. Slides were reviewed and analysed by two pathologists independently. They were blinded to final outcome. Each case was allocated a category according to both EIS and PSRUC system (Table 1) and was compared. In cases of discrepancies, consensus was obtained under multi-head microscope examination.

In PSRUC, cases with benign cytologic features or those with mild cytologic atypia with a known cause like polyomavirus infection, urolithiasis, irradiation, chemotherapy or instrumentation were included in NHGUC. Tissue fragments without cytologic atypia were also included in this category. Presence of cells with nuclear / cytoplasmic N / C ratio of more than > 0.5 alone would also qualify for this category. AUC category is assigned after excluding degenerated and superficial urothelial cells. Urothelial cells with increased N / C ratio (> 0.5), and one of the following features: nuclear membrane irregularity, nuclear hyperchromasia and coarse clumped chromatin were considered under AUC. Presence of atypical cells with degenerative features also deserves AUC even with the defined nuclear abnormalities. Cytological findings are similar for both SHGUC and HGUC except for quantitative cut off of ten cells (< 10 cells for SHGUC, ≥ 10 cells for HGUC). In both categories, cells should display N / C ratio of > 0.7, moderate to severe hyperchromasia and at least one of the two following features: irregular nuclear membrane and irregular clumped chromatin.

EIS differed from PSRUC in certain aspects. It included five diagnostic categories. In atypical cell category, even degenerated cells with mild cytologic atypia were included without objective criteria. Cells displaying mild reactive atypia were also included in atypical category. Criteria for diagnosing SHGUC and HGUC were not much different from PSRUC except for well-defined qualitative and quantitative guidelines.

Cytology diagnosis was correlated with histopathology wherever available. Specimens for histopathologic examination were obtained by Transurethral Resection of Bladder Tumor in most of the cases. Cold cup bladder biopsy was available in a few cases. Interval of maximum 1 year duration was considered valid between cytology and follow up cystoscopic biopsy, as longer interval may interfere with study results. In cytohistologic correlation of cases with multiple urine samples, specimen with worst category was taken as representative.

Statistical Analysis

Data was analysed using statistical tests for sensitivity, specificity, accuracy of urine cytology in detecting malignancy. Positive Predictive Value (PPV) for diagnostic categories of both systems in predicting subsequent high-grade urothelial carcinoma on histopathology was calculated using SPSS 19 software.

RESULTS

A total of 74 cases with urogenital symptoms were included in the study. 50 % of cases had three consecutive urine samples. 66 were males and 8 were females, with male to

female ratio of 8:1. Age ranged from 4 to 78 years (mean age = 70 year). 2 patients were < 10 year old. Age ranged from 38 - 78 years for patients with urothelial carcinoma. 7 patients were under carcinoma bladder surveillance. A total of 9 cases were of high grade urothelial carcinoma. Dysuria (44 %) and haematuria (33 %) were the most common clinical presentation. Bladder mass was the commonest cystoscopy finding (~ 32 %). Number of cases assigned to different categories according to EIS and PSRUC are shown in Table 1.

Histopathology findings were available in 21 cases. Amongst these 5 cases were non-urothelial lesions (one case each of renal cell carcinoma, rhabdomyosarcoma, Wilms tumor, two cases of benign prostatic hyperplasia), hence, excluded. Correlation between histopathology and cytology findings in 16 cases along with PPV for high grade urothelial carcinoma is shown in Table 2.

EIS	Number of Cases n = 76 (%)	PSRUC	Number of Cases N = 76 (%)
Non diagnostic / Unsatisfactory	02 (2.6)	Non diagnostic / Unsatisfactory	02 (2.6)
Negative for Malignancy	60 (79)	Negative for High Grade Urothelial Carcinoma (NHGUC)	64 (84.2)
Atypical cells	08 (10.5)	Atypical Urothelial Cells (AUC)	03 (3.4)
Suspicious for High Grade Urothelial Carcinoma	04 (5.2)	Suspicious for High Grade Urothelial Carcinoma (SHGUC)	04 (5.2)
Positive for malignant cells / High Grade Urothelial Carcinoma	02 (2.6)	High Grade Urothelial Carcinoma (HGUC)	02 (2.6)
		Low Grade Urothelial Neoplasm (LGUN)	00
		Others	01 (1.3)

Table 1. Diagnostic Categories and Number of Cases According to EIS and PSRUC

(EIS: Existing Institutional System, PSRUC: Paris System of Reporting Urine Cytology, LGUN: Low Grade Urothelial Neoplasm, HGUC: High Grade Urothelial Carcinoma, NHGUC: Negative for High Grade Urothelial Carcinoma, PPV: Positive Predictive Value)

Histopathology Diagnosis	Cytology Categories Using EIS and PSRUC							
	NHGUC		Atypical		Suspicious		HGUC	
Categories & No. of Cases (n = 16)	EIS (n=07)44 %	PSRUC (n=09) 56 %	EIS (n=03) 19 %	PSRUC (n=01) 06 %	EIS (n=04) 25 %	PSRUC (n=04) 25 %	EIS (n=02) 12.5 %	PSRUC (n=02) 12.5 %
Benign-01	00	01	01	00	00	00	00	00
*LGUN-06	04	06	01	00	01	00	00	00
†HGUC-09	03	02	01	01	03	04	02	02
PPV of HGUC (%)	42.8	22.2	33.3	100	75	100	100	100

Table 2. Correlation between Histological and Cytology Findings Using Institutional Classification System

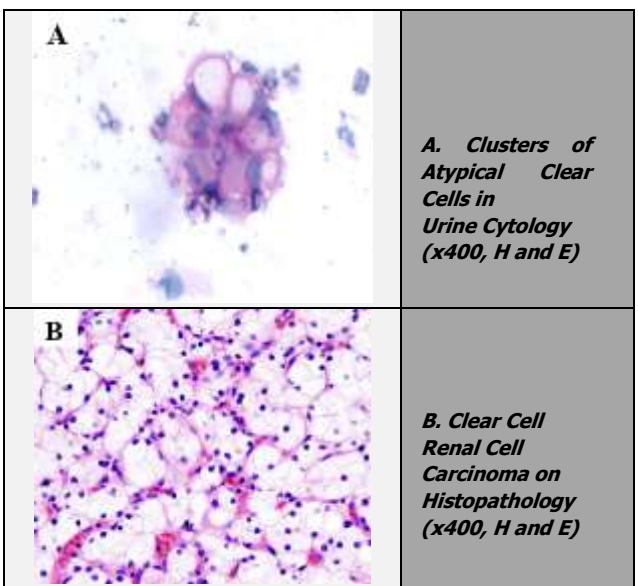
(*LGUN (Low Grade Urothelial Neoplasm) includes papilloma, papillary neoplasm of low malignant potential, low grade urothelial carcinoma on histopathology)
(†HGUC (High Grade Urothelial Carcinoma) includes non-invasive high grade papillary urothelial carcinoma, invasive urothelial carcinoma and urothelial carcinoma in situ on histopathology)

Sensitivity, specificity and accuracy of urine cytology in detecting malignancy using PSRUC was 66.67 %, 100 % and 81 % respectively. With EIS, sensitivity was 55.5 %, specificity was 85.71 % and accuracy 68.75 %. PSRUC resulted in increase in cases assigned to NHGUC (79 % vs. 84 %) and reduction in number of cases assigned to AUC category (10.5 % vs. 3.4 %). Performance of AUC category showed significant difference between two systems. In EIS 33 % of AUC cases were associated with subsequent high-grade urothelial carcinoma on histopathology. The rate increased to 100 % using PSRUC. None of the cases of low-grade urothelial carcinoma were diagnosed as AUC using PSRUC compared to EIS where 33 % each was included in atypical and suspicious category. There was no difference found in PPV for SHGUC / HGUC in both classification systems.

Name of the Study	Classification System	Positive Predictive Value for High Grade Urothelial Carcinoma (%) NHGUC	AUC	SHGUC	HGUC
Hassan et al[17] n = 124	EIS	26	33	91	96
	PSRUC	18	53	83	100
Malviya et al[18] n =34	EIS	36.3	83.3	100	90.9
	PSRUC	45.4	50	75	94.1
Present Study n = 16	EIS	43	33	75	100
	PSRUC	22	100	100	100

Table 3. Performance of Institutional Systems and PSRUC in Predicting High Grade Urothelial Carcinoma in Different Studies

(EIS: Existing Institutional System, PSRUC: Paris System of Reporting Urine Cytology, NHGUC: Negative for High Grade Urothelial Carcinoma, AUC: Atypical Urothelial Cells, SHGUC: Suspicious of High-Grade Urothelial Carcinoma, HGUC: High Grade Urothelial Carcinoma)



A. Clusters of Atypical Clear Cells in Urine Cytology (x400, H and E)

B. Clear Cell Renal Cell Carcinoma on Histopathology (x400, H and E)

Figure 1. Urine Cytology and Histopathology in Clear Cell Renal Cell Carcinoma

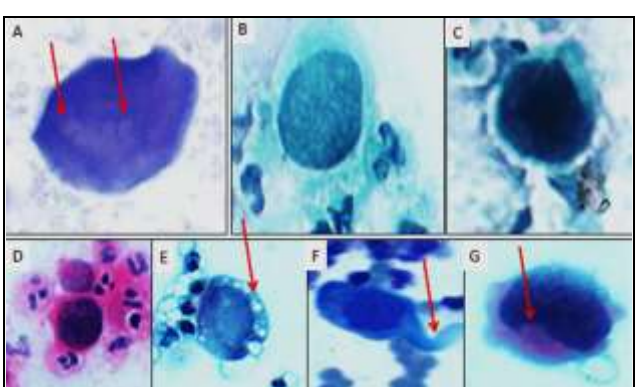


Figure 2. Nuclear Cytomorphology in HGUC and SHGUC

Figure 2. A: Nucleolar prominence (X400, Leishman); B, C- Increased N/C ratio, nucleolar prominence (x400, Pap); D- Tumour cell admixed with neutrophils (x400, H and E); E: Cytoplasmic vacuolation (x400, Pap), F: Tadpole cell (X400, Leishman); G: Irregular nuclear contour (x400, H and E).

Five cases of non-urothelial lesions showed atypical cells in urine cytology with EIS. However, with PSRUC two cases were assigned to NGUC. Two cases of benign prostatic hyperplasia and one case of clear cell renal cell carcinoma (RCC) remained in AUC. Two cases of genitourinary tuberculosis were diagnosed by using Ziehl Neelsen staining on urine cytology.

DISCUSSION

Urine cytology is one of the most commonly used inexpensive and non-invasive clinical investigations. It is widely used screening tool in evaluation of patients with urogenital symptoms.

We evaluated urine cytology of 74 patients with urogenital symptoms. Median age was 62 years. Male predominance was noted. Median age for patients with high grade urothelial carcinoma was 67 years. Majority of these patients presented with hematuria (~ 77 %), concordant with other studies.[7-9]

With the implementation of PSRUC, allocation of cases in different diagnostic categories changed in comparison to EIS. There was a reduction in the reporting of AUC category in PSRUC (3.4 %) when compared to EIS (10.5 %). Such reduction in AUC using PSRUC was reported in other studies, where rates ranged from 1.9 % to 23.2 %.[10-12]

Four out of eight cases (50 %) of AUC were re-categorised into NHGUC using PSRUC, which led to increase in NHGUC (by 5 %) and reduction in AUC (by 7 %). These changes are in accordance with other studies.[9,13] Presence of atypical cells in urine due to infection, urolithiasis and treatment effect should no longer be considered as AUC according to PSRUC. Bacterial infections are characterised by reactive urothelial cells having prominent nucleoli admixed with sheets of neutrophils. Presence of decoy cells having large homogeneous basophilic inclusions is diagnostic of polyomavirus infection. In addition, presence of smooth nuclear contour differentiates it from malignant cells. Urine cytology may show pseudopapillary clusters in patients with urolithiasis. These clusters are characterised by the presence of cytoplasmic collars. Radiation induced changes include significant cytomegaly, nucleomegaly, nuclear and cytoplasmic vacuoles. However, nucleocytoplasmic ratio will be maintained. Reactive umbrella cells and seminal vesicle cells can be misinterpreted as AUC. However, reactive changes attributable to particular aetiologic factors should be assigned NHGUC according to PSRUC.[14] PSRUC states mild cytologic atypia without significant clinico-radiologic and cystoscopy findings should be assigned NHGUC.

However, reduced reporting rate of AUC using PSRUC might compromise early diagnosis of HGUC.[15,16] One case of AUC by PSRUC turned out to be high grade urothelial carcinoma on histopathology in our study. Difficulty in precise assessment of N / C ratio in the absence of digital morphometry and lack of defined guidelines for assessment of atypical cytological features associated with inflammation, degeneration and crystals compromises the diagnosis of HGUC. Relying only on nuclear hyperchromasia as one of the major criteria in diagnosing HGUC, ignoring other associated cytomorphological characters typical of malignancy could be an additional factor.[16]

Non urothelial lesions can show atypical cells in urine cytology.[17] In the present study, one case of clear cell renal cell carcinoma (RCC) (Figure 1), two cases of benign prostatic hyperplasia showed atypical cells. According to PSRUC atypical cells in non-urothelial lesions were assigned a separate category. EIS lacked this category resulting in increased AUC cases.

There was no difference found in predicting high grade urothelial carcinoma on histopathology in cases assigned to SHGUC and HGUC by using PSRUC. However, the rate of detection of SHGUC increased by 25 % with the use of PSRUC. With EIS one SHGUC case turned out to be low grade urothelial neoplasm on histopathology. This could be due to lack of well-defined quantitative criteria used for diagnosis of SHGUC.

The PPV percentage for high grade urothelial carcinoma was highest for the HGUC and SHGUC (100 %), which is concordant with other studies.[18,19] Risk of malignancy for NHGUC category was found to be 22 %. Other studies have observed a range of 0 - 10 % risk. However this range is influenced by sample size and varied standards of institutional reporting systems. Comparison of performance of both reporting systems with other studies is shown in Table 3.

In PSRUC presence of high N / C ratio > 0.7, nuclear pleomorphism, nuclear membrane irregularity, and severe hyperchromasia were considered as definitive nuclear features suggesting SHGUC / HGUC.[6] We also observed nucleolar prominence, cytoplasmic vacuolations, tadpole cells in cases of HGUC (Figure 2) as observed by Renshaw et al.[20]

Implementation of PSRUC resulted in reduction of incorrect assignment of Low Grade Urothelial Neoplasms into atypical or suspicious category. PSRUC requires cellular fragment with fibrovascular core and mild cytologic atypia falling short off HGUC to designate LGUC.[19] However, in EIS presence of subtle cytological abnormalities due to reactive atypia or polyomavirus induced changes were also placed in atypical / suspicious category.

PSRUC resulted in improved sensitivity (66.6 %) and specificity (100 %) when compared to EIS (sensitivity - 55.5 %, specificity - 85.71 %) in detection of malignancy. Diagnostic accuracy increased from 68.75 % in EIS to 81 % in PSRUC. Overall predictive value for malignancy increased from 83.33 % in EIS to 100 % in PSRUC. This enormous improvement in predicting malignancy in PSRUC in urine cytology could be due to limited number of cases available for cytohistologic correlation in our study. Sharada et al.[9] reported sensitivity of 83.3 %, specificity of 89.4 % and diagnostic accuracy of 86.52 %. Malviya et al.[19] found a higher sensitivity of 95 % and an accuracy of 86.2 % by using PSRUC. Diagnostic accuracy was comparable in all three studies.

Routine use of Ziehl-Neelsen (ZN) staining in urine cytology helps in early diagnosis of urogenital tuberculosis and decreases rate of AUC. Khalid et al.[21] reported 25 % specificity and 100 % sensitivity of urine cytology in

diagnosing tuberculosis. In our study,[22] two cases of urogenital tuberculosis clinically suspected to be malignant were diagnosed on urine cytology. Diagnosis of genitourinary tuberculosis (GUTB) is based on combination of clinical signs, cytology and ideally on a positive ZN stained smears or urine culture.[21]

This study is limited by its retrospective nature and limited sample size. Urine cytology interpretations were done irrespective of urine sampling methods. Several pathologists of institute were involved in diagnosis of urine cytology of study cases initially, which might have caused interobserver variability. Whereas only two pathologists were involved in recategorization according to PSRUC, would have resulted in increased performance of PSRUC. Nuclear-cytoplasmic ratio was assessed using eyeballing. Digital image analysis ensures accurate quantification of cells and N / C ratio, hence correct categorization. Hang et al.[23] found that identification of AUC with N:C ratio > 0.486 has a high predictive power for high grade urothelial carcinoma on biopsy. Independent validation of cut off value for N:C ratio by laboratories is essential as this ratio also depends on cytopreparatory techniques used. Additional large studies with clinical follow-up are needed to further investigate the impact of combining two diagnostic categories.

CONCLUSIONS

Implementation of PSRUC resulted in decreased number of AUC cases and increase in NHGUC. PSRUC improves predictive accuracy of subsequent high-grade urothelial carcinoma on histopathology. Further, it ensures uniformity in urine cytology reporting by defined set of guidelines. Judicious use of urine cytology might aid in early diagnosis of infectious conditions like tuberculosis.

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