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The Paris System for Reporting Urinary Cytology: A pathologist's experience from a tertiary care center

[1]Lovelesh K Nigam, M.D. (Path), P.D.C.C. (Renal and Transplant Path), Assistant Professor, Department of Pathology, Lab Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

[2]Aruna V Vanikar, Professor and Head, Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

[3]R. D. Patel, Professor, Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

[4]Kamal V Kanodia, Professor, Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

[5]K. S. Suthar, Associate Prof., Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

Corresponding Author: Lovelesh K Nigam, M.D. (Path), P.D.C.C. (Renal and Transplant Path), Assistant Professor, Department of Pathology, Lab Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

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Abstract

Introduction: Urothelial carcinoma is the ninth most common malignancy worldwide and urine is easily accessible for cytology and inexpensive tool for diagnosis. However the sensitivity was low due to lack of a standardized reporting system. The Paris system for urinary cytology was introduced to minimize interobserver variability.

Materials and methods: Institutional based study over period of 3 years and findings were categorized according to Paris system. Demographic and cytological findings were studied with respect to each category.

Results: 676 UC specimens were received from 533 patients. The M:F ratio was 1:4.4. Category 1, 2, 3, 4 and 5 included 177(33.2%), 206(38.6%), 77(14.4%), 38(7.12%) and 16(3.01%) cases respectively. The overall sensitivity of UC in diagnosis of urothelial malignancy was 97.7%.

Conclusion: UC is an important tool that aids in diagnosis of bladder cancer with a higher sensitivity for high grade carcinoma. Correlation with clinical and cystoscopy findings increases the sensitivity of UC.

Introduction

Urinary bladder cancer is the ninth most common cancer worldwide, and the second most common genitourinary malignancy, also accounting for 3.9% of all cancer cases in men.(1,2) Patients with muscle invading tumors have poor prognosis, with only 30% surviving 5 years despite extensive treatment.(2,3) Early diagnosis is the key for increasing 5-year survival of these patients. (4) Bladder cancer can be diagnosed by cystoscopic evaluation followed by a biopsy, urine cytology and urinary biomarkers. Urine cytology (UC) is a non-invasive, cheap and readily available tool to diagnose bladder cancer.(4,5) Lambl (1856), Beale (1864) and Sanders (1864) were among the first to report extensively on identifying cancer cells in the urine.(5) An important diagnostic principle of UC is 'higher the grade of tumor, more accurate is the diagnosis on UC'.(6) It has long been known that UC is accurate in the diagnosis of high-grade urothelial carcinoma (HGUC) with cyto-histological correlation reported as high as 98%, sensitivity of nearly 90% and specificity of 98% to 100%. In contrast, it carries a much lower diagnostic yield for low-grade urothelial neoplastic lesions (sensitivity: 8.5% and specificity of 50%). (7,8) Advantages of UC include ease of procurement and the ability to evaluate the entire urothelial tract at a considerable low cost.(2) The accuracy of UC depends on several factors mainly related to tumor grade, the nature of specimen, and sampling. Moreover, the specimen type also seems to impact the predictive value of UC, with voided specimens being more specific and slightly less sensitive than instrumented specimens due to absence of the instrumentation-induced reactive changes.(8) Sensitivity of 41%, 41% and 60% has been reported, respectively for one, two, and three voided urine specimens.(7)

The sensitivity of UC is better for patients with gross hematuria and reported to have the highest incidence of prediction of urinary malignancy (estimated range, 20%-25%).(9) Urinary sepsis and degenerative changes detected in the exfoliated tumor cells markedly mask and interfere with positive cytological diagnosis. (10)

Several classification schemes for reporting UC have been proposed since the time when its usefulness was described about 60 years ago by Papanicolaou and Marshall.(5) Establishing a clinically useful scheme for reporting UC has been challenging, and some of the weaknesses of prior classification schemes include lack of rigorous definition of validated cytologic criteria for specific categories, lack of consensus for atypical categorization, and lack of broad acceptance and use by the general pathology community.(3,5,11) So an international tele-cytologic quiz on UC was conducted by Glatz et al.(11) Nearly 48.4% participants misdiagnosed HGUC as a reactive lesion, 54.5% misdiagnosed viral cytopathic effect as high grade, 79.2% misdiagnosed basal cells in bladder wash as atypia and 64% misdiagnosed low grade atypia as benign.(11) Specialists interested in UC to establish a new uniform reporting system for US were encouraged with the success and widespread international

acceptance of The Bethesda System for cervical cytology. Thus in the 18th International Congress of Cytology held in Paris in May 2013, a panel of cytopathologists, surgical pathologists and urologists established a new reporting system for UC. This system concentrates on detecting HGUC mainly and minimizes the detection of low grade urothelial carcinoma (LGUC) on cytology, because cytological sensitivity is high for the former and is questionable for the latter.(10,11,12) The low sensitivity for LGUC is because these lesions yield very few cells, the cells are morphologically closely similar to normal benign urothelium and universal morphological criteria could not be made.(14).

With these developments in UC at the international level, we decided to conduct a study to present our experience of reporting UC in accordance with the 'Paris system for classifying UC'.

Material And Methods

This was an Institutional review board approved retrospective study of UC of samples received from urology department, from January 2017 to December 2019. We included only the initial UC for evaluation and UC performed for follow-up studies were evaluated separately. Correlation with surgical pathology was done in a subset of cases depending on the availability. Demographic profile included age, sex and indication for UC. Samples from nephrology and transplantation units were excluded.

Sample collection and preparation

The second morning voided sample was collected in a clean, sterile, disinfectant/detergent free container. The urine sample was processed in two phases, one for phase contrast microscopy and the other part was subjected to cytospin preparation.

(A) Preparation of sediment for phase contrast microscopy: Once received, 1 ml of urine sample was transferred to a 5 ml test-tube with an equal quantity of ether alcohol and centrifuged at 1000 RPM for 10 minutes. The supernatant was discarded and the urine sediment was subjected for phase contrast microscopy for presence of type of epithelial cells, red blood cells, leucocytes and microorganisms.

(B) Cytospin preparation: Remaining urine sample was subjected to cytocentrifuge at 1000 RPM for ten minutes by Cytospin method using Millipore (Millepore Corporation, Billerica, MA) filters. The cytospin slides were fixed in alcohol. One slide was stained with Hematoxylin and eosin stain and other with Papanicolaou stain according to the standard protocols. The stained slides were evaluated by a panel of five cytopathologists and was reported according to the Paris system of reporting urinary tract cytology described below.

The Paris System for reporting urinary tract Cytology: (12)

Adequacy: If atypical, suspicious or malignant cells were seen in any number the sample was considered adequate. In absence of atypical, suspicious or malignant cells, adequacy was defined if there was appropriate benign urothelial cellularity.

Categories of the Paris System:

1. **Unsatisfactory/Non diagnostic:** Absence of atypical, suspicious or malignant cells or presence of excessive inflammatory cells or only degenerated cells, obscuring the urothelial cells.

2. **Negative for HGUC (NHGUC):** Presence of benign glandular cells, squamous cells originating in squamous metaplasia of urothelium or external genital tract skin, benign seminal vesical cells, changes

associated with urolithiasis or treatment-related changes.

3. **Atypical urothelial cells(AUC):** Cells that fulfill one major and one minor criterion from the following features:

1. Major criterion: Presence of non-superficial and non-degenerated urothelial cells with increased nuclear cytoplasmic (N/C) ratio (>0.5).

2**.** Minor criteria**:**

(1) Mild nuclear hyperchromasia

(2) Irregular nuclear membranes (chromatin rim or nuclear contour)

(3) Irregular, coarse, clumped chromatin

4. **Suspicious for HGUC:** Cells that fulfill one major and one minor criteria:

1. Major criteria: Presence of non-superficial and non-degenerated urothelial cells with an increased N/C ratio (>0.7) and severe nuclear hyperchromasia.

2. Minor criteria

(1) Irregular nuclear membranes (chromatin rim or nuclear contour),

(2) Very dark, irregular, coarse, clumped chromatin.

5. **HGUC:** Smear comprising of a minimum of 5 to 10 severely abnormal urothelial cells with an N/C ratio of 0.7 or greater, showing moderate to severe hyperchromasia, coarse chromatin, and markedly irregular nuclear membrane.

6. **Low Grade Urothelial Neoplasm:** Presence of fibrovascular cores lined by atypical urothelial cells.

7. **Other Malignancies- Primary, Metastatic and Miscellaneous lesions:** Cytological features reveal findings consistent with squamous cell carcinoma (SCC), adenocarcinoma, small-cell carcinoma, secondary malignancies or cells from distant metastases (malignant melanoma, carcinomas of stomach, breast, kidney and lung).

Statistical Analysis

All continuous parameters were expressed as mean±1 SD and qualitative variables as proportions. Sensitivity was calculated using the following formula= True positive/ true positive +False negative.

Results

A total of 676 UC specimens were received from 533 patients over a period of three years. Follow-up samples were received from 94 patients. Males outnumbered females, there were 436 males and 97 females (M:F: 1:4.4). Mean age was 56.2±14.7 years (Range: 5 – 82 years). Maximum number of patients were in the age group of 50-60 years [n= 135 (26.4%), 114 males, 24 females] followed by patients in age group of 60-70 years [n= 125 (23.4%), 101 males, 24 females] and > 70 years [n= 94 (17.6%), 89 males, 5 females]. Four (0.75%) patients were of age < 20 years.

Indication for UC:

The most common indication was hematuria followed by bladder mass observed on radiological examination. Hematuria was noted in 36(6.75%) cases and bladder mass was noted in 28(5.25%) cases. UC was performed in 24(4.5%) cases as a pre-operative investigation. These patients were operated for non-bladder pathology including nephrectomy (3.1%) and prostate biopsy (1.31%). Ninety four (17.63%) cases had been diagnosed with urothelial carcinoma and UC in these cases was performed as a part of routine follow-up.

Category 1: Unsatisfactory/Non diagnostic

Out of 533 cases, 177 (33.2%) UC were reported as non-diagnostic. The mean age in this category was 54.4±15.07 years and sex ratio was 7:1 (males: 148; females: 29). The youngest patient was 17 years and the eldest was 90 years old. Hematuria was noted in 15 (8.4%) cases along with inflammation, and isolated hematuria was observed in 7 (3.9%) cases. Of 177

cases, 69 (38.9%) were reported inadequate due to presence of neutrophils suggestive infection. Histopathology was available for correlation in 65(36.7%) cases of this category. Three (1.69%) cases were reported as cystitis. Urothelial carcinoma was reported in 50(28.2%) cases, of which 40(22.5%) were reported as LGUC and 10(5.6%) as HGUC. Three (1.69%) cases of non-urothelial carcinoma were also reported, 1(0.56%) was round cell carcinoma and 2(1.12%) were that of SCC. UC was performed as a preoperative procedure in 9(5.08%) cases [6 cases of renal cell carcinoma (RCC), 1 case each of leiomyoma, benign adenofibromyomatous hyperplasia of prostate (BPH) and prostatic adenocarcinoma respectively].

Category 2: NHGUC

This was the most common diagnosis reported in 206(38.6%) cases. The mean age in this group was 54.9±14.3 years, 158 were males and 48 were females (M:F:3.2:1). Hematuria was present in 25(11.9%) cases. Inflammatory cells comprising of neutrophils were noted in 148(71.8%) cases. Hematuria along with neutrophils was noted in 19(12.8%) cases. 82(39.8%) cases underwent biopsy in this category. Benign conditions of non-specific cystitis were noted in 13(15.8%) cases, eosinophilic cystitis in 2(2.4%), cystitis cystica in 3(3.6%) and giant cell reaction in 1(1.2%) case. LGUC and HGUC were noted in 41(50.8%) and 5(6.09%) cases respectively. UC revealed plenty of neutrophils in 31(75.6%) out of 41 cases with a histological diagnosis of LGUC. Hematuria was present in 14(34.1%) cases out of these 41 along with neutrophils. Cytology of all HGUC cases revealed neutrophils with RBCs along with degenerated cells. Four cases of non- urothelial tumor were reported of which 2 cases were paraganglioma, and one each of metastatic RCC and carcino-sarcoma. In 10(12.2%) cases of this category, UC was performed as a pre-operative investigation. These were reported to have prostatic adenocarcinoma (2 cases), ADPKD (2 cases), RCC (3 cases), chronic pyelonephritis (2 cases), BPH (3 cases) and balanitis (1 case).

Category 3: AUC

77(14.4%) cases belonged to this category. Mean age was 60.1±12.5 years, 67 were males and 10 were females (M:F: 6.7:1). Hematuria was noted in 37(48.05%). Bladder mass was present in 18(23.3%) cases on radiology. Histological data was available in 69(89.1%) cases for correlation. LGUC was reported in 45(58.4%) and HGUC in 13(16.8%) cases. Acute inflammation in the form of presence of neutrophils was seen in 22(28.5%) cases of LGUC and 4(5.1%) cases of HGUC. Both hematuria and pyuria were noted in 12(15.5%) cases with LGUC and 3(3.8%) cases with HGUC. SCC was noted in 1(1.2%) case which had concomitant pyuria and hematuria. In 9(11.6%) cases UC was performed as a preoperative investigation (Prostatic adenocarcinoma: 4 cases; RCC: 4 cases, Wilm's tumor: 1 case). Cystitis was reported in 2(2.5%) cases with cytological diagnosis of atypia.

Category 4: Suspicious for HGUC

38(7.12%) cases belonged to this category. Mean age in this group was 63.02±12.77 years, 34 were males and 4 were females (M:F:8.5:1). Hematuria was noted in 32 (84.2%) cases. Neutrophils with RBCs were seen in 18(47.3%) cases. Histological diagnosis was available in 29(76.3%) cases. LGUC was reported in 16 (42.1%) cases, and 14 (87.5%) out of 16 cases had hematuria. All 11 (28.9%) cases of HGUC had hematuria. One (2.6%) case each of small round cell tumor and cystitis cystica were also reported. In 3(7.8%) cases, histology revealed a benign lesion, but cytology was reported as suspicious of HGUC.

Category 5: HGUC

HGUC was reported in 16(3.01%) cases. Mean age was 64.31±10.2 years. 15(93.7%) were males and 1(6.25%) was female in this category. Hematuria was present in 14(87.5%) cases and neutrophils were present along with RBCs in 5(31.2%) cases. Histopathology was available in 15(93.7%) cases of which 4(25%) were reported as LGUC and 11(68.7%) as HGUC.

Follow-up cases:

Ninety four patients underwent UC for follow-up. 57 out of these 94 cases reported as urothelial carcinoma (42 cases: LGUC; 15 cases: HGUC) underwent UC twice, 19 cases (12 cases: LGUC; 7 cases: HGUC) thrice, 8 cases (LGUC: 5 cases; HGUC: 3 cases) four times and 3 cases (LGUC: 2 cases; HGUC: 1 case) underwent UC five times. Two patients underwent follow-up UC nine times, 1 underwent six times, 1 for seven times and one case for ten times. Of these, three (3.2%) patients developed recurrent LGUC. UC was reported as 'presence of atypical cells' (category 3) in all 3 patients. These 3 patients subsequently underwent biopsy and were reported to have LGUC. Remaining cytological diagnosis was suggestive of features of category 2 and hence was not re-biopsied.

Discussion

Bladder cancer is one of the most common malignancies occurring worldwide. It represents 13th most common cause of all cancer deaths worldwide. Most of the bladder cancers are non-muscle invasive or muscle invasive urothelial cell carcinoma of low histological grade. (3)UC is an essential modality for the detection of urothelial neoplasia. Cytology is also essential for evaluation of patients with genitourinary symptoms, especially hematuria, and as a surveillance tool for patients with a history of bladder cancer.(8) Paris system of reporting urinary tract cytology became a popular universal standard reporting facility since May 2013.(11,13)

Most of the studies have reported a higher incidence of malignancy in the age group above 50 years. Mean age of presentation in our study was 52.8±16.4 years. Mady et al reported that the incidence of urothelial carcinoma was higher in patients above 50 years of age, with a mean of 64 years (range: 50-88 years).(10) Similarly Fiefer et al reported a median age of 64 years in a study of 200 patients. (15) Malviya et al reported a mean age of 52.8 years in their cohort of 176 patients.(13) Our observation is similar to these studies. We too reported higher incidence of atypical or malignant cytology in patients above 40 years of age. Nearly 41.03% patients were > 60 years of age in our study having cytology consistent with malignancy. According to Chawla et al urinary bladder tumors are commonly seen in 5th –7th decade of life and they reported 109 cases (96.46%) who were above an age of 60 years.(4)

Urothelial malignancies are more common in males due to various lifestyle-related risk factors such as smoking and occupational exposure. In study by Mady et al (n=152), 133 were males and 19 were females. (10) Similarly male predominance of 132, 700 and 131 males was reported by Fiefer et al, Nabi et al and Malviya et al respectively.(13,15,16) Their results were similar to our study. We also reported a male preponderance.

Hematuria was the commonest indication for UC in most of the studies.(10,13,15) Mady et al reported microscopic hematuria in 37 patients and gross hematuria in 115 patients.(10) Nabi et al in their study of UC on 900 patients over 15 months reported hematuria in 62% patients.(16) Similarly in the study by Malviya et al, hematuria was the most common

feature (100%).(13) Sidappa et al however reported a lower incidence of hematuria of 6.6%.(3)

Mady et al observed that in patients above 50 years of age, who present with hematuria and bladder lesion on ultrasound were at high risk for presence of urothelial carcinoma.(10) Viswanath et al. also emphasized that sensitivity of UC is better in those patients who present with gross hematuria.(17) In our study we observed hematuria in all categories. The incidence of hematuria was 7.8% in our study. In category 3, 4 and 5 the incidence of hematuria was 48.05%, 84.2% and 87.5% respectively. We also observed hematuria in patients of category '1' (10.28%) and category '2' (24.1%) and these were reported to have urothelial carcinoma on biopsy. When we looked for radiological findings in these cases after biopsy, we found that 30.8% of these cases showed presence of bladder mass. Thus our study infers that if hematuria is noted, either macroscopic or microscopic, it requires aggressive evaluation and correlation with radiological findings.

Presence of acute inflammation is another common finding on UC. Sidappa et al reported acute inflammation in 33.6% cases. (3) In study by Mady et al, 84 out of 152 patients revealed neutrophils on cytology.(10) Acute inflammation was noted in 279(52.3%) patients in our study. Higher incidence of acute inflammation could possibly because of higher incidence of infection of the urogenital tract in our country (18). Of the 20 cases reported as cystitis on histology, cytology in 15 (75%) patients revealed acute inflammation in the present study.

Mady et al have reported an incidence of positive cytology of 44.1%.(10) Similarly Fiefer et al reported an incidence of 11.5% of atypical cytology.(15) The incidence of positive cytology in our study was 24.5%. If we group overall incidence of positive cytology in our study according to the Paris system, 58.7% belonged to category '3', 29 % to category '4' and 12.2% to category '5'. Nabi et al reported an incidence of 20.36% of positive cytology.(16) They did not follow the Paris system and reported almost 11.35% cases having an indeterminate urinary cytology. Sidappa et al reported an incidence of 32.5%.(3) Rai et al reported UC in accordance with the Paris system: category '3' in 11.1%, category '4' in 17.8% and category '5' in 11.1%. They also reported cases of low grade urothelial neoplasm (5.6%) and one case of category '7'.(19) Findings of Bakkar et al were 54 (54%) NHGUC, 23 (23%) AUC, 9 (9%) SHGUC, and 14 (14%) HGUC in 100 patients.(20) We did not report any cytology that was consistent with category '6' (low grade urothelial lesion). However we did report one case of metastatic RCC in a 60 year old patient, who had undergone radical nephrectomy for clear cell RCC two years back.

The incidence of samples in the non-diagnostic category was 33.2% (177 cases) in our study, 53 (43.5%) cases of this group had either LGUC (34.1%) or HGUC (8.5%) and all of them presented with hematuria. Literature suggests that the diagnostic yield for LGUC is very low.(3,10) Poor patient compliance could possibly be another reason in our study since most of the patients served by our institute belong to low socio-economic strata. Improper sample collection leading to cellular degeneration before fixation, delay in receiving the sample and lack of knowledge of giving a proper sample are some more factors documented. So we suggest that in cases of hematuria with cytology consistent with ND category, a policy of repeat sampling is necessary. Several studies have shown that the number of samples increases the sensitivity of UC, especially in the detection of high-

grade lesions.(8) However we did not get any repeat samples, biopsy was performed in these patients.

The overall sensitivity of UC in diagnosis of urothelial malignancy was 97.7% in our study. Mady et al reported a lower sensitivity of 53.4%. (10) Sidappa et al reported a sensitivity of 98.5% similar to our study.(3) Rai et al reported a sensitivity of 83.33% in their study where they compared the Paris system with the six tier system (sensitivity: 57.50%) they were following in their institute.(19)

The specificity of UC in our study was low. We report a specificity of 28.9% in contrast to high specificity reported by Rai et al (89.4%), Sidappa et al (74.5%) and Mady et al (94.7%).(3,10,19) We report a diagnostic accuracy of 70.4% in our study which is comparable to the study by Sidappa et al (76.8%).(3) When we consider the diagnostic accuracy in category '3', '4' and '5' the diagnostic accuracy increased to 97.1%. The discordance in specificity and a slightly low cytological and histological discordance in our study could possibly be due to higher number of cases of urothelial carcinoma in category 2. This could possibly be attributed to the concomitant presence of acute inflammation in most of the cases. About 75.6% of 41 patients with a histological diagnosis of LGUC and all five (100%) cases with histology of HGUC, showed smears with plenty of neutrophils. When we reviewed the smears of all these cases, the epithelial cells were obscured by inflammatory cells. Various studies have shown that difficulties do arise in patients with inflammatory conditions, concurrent urinary infections or stones and patients with indwelling catheters.(16) However a cystoscopy and radiological correlation would aid in proper diagnosis.

In our study we did not report any case of category '6'. However on histology we reported 40, 41, 45, 16 and 4 cases of LGUC in categories 1, 2 3, 4 and 5 respectively. This could possibly be due to the strict definition for LG urothelial neoplasm category which is characterized by presence of papillary cell fragments with fibrovascular cores with cells revealing mild atypia. We did not report this finding on cytology and so refrained to give the cytological diagnosis of LG urothelial neoplasm. We reported more cases of HGUC in category '4' and '5', suggesting UC had a higher sensitivity in determining HGUC. This finding is in concordance with various other studies. Rai et al also reported lowest sensitivity of UC in detecting low-grade tumors. They stated that cellular atypia present in these tumors is minimal to moderate which can also be due to presence of degenerative changes, instrumentation effect, lithiasis, reactive changes, therapy changes and viral cytopathic effect.(19) Accuracy of diagnosing malignancy by cytology is highly variable and depends on the presence of diagnostic yield, processing of the sample, and expertise of the cytopathologist. Diagnosis is also more difficult in low-grade noninvasive carcinoma since the sensitivity of detection of malignant cells is very low. False positivity can be seen in patients with reactive changes secondary to infection, stone, previous instrumentation, and intravesical therapy. (2,3)

The positive predictive value (PPV) and negative predictive value (NPV) of UC in our study was 86.9% and 72.9% respectively. Rai et al in their study of 90 cases reported a PPV of 87.50% and NPV of 85.70%.(19) A slightly lower NPV could possibly be due to the higher number of false negative cases in our study. Three cases of cystitis cystica on biopsy were reported as atypical category (2 cases) and suspicious of HGUD (1 case) on cytology.

In our study we reported SCC and small round cell tumor of the bladder. However all these cases were reported as category '1' (2%) or '2' in our study. Only one case each was reported to have cytology consistent with class '3' or '4'. Thus in our experience we did not find UC diagnostic in these tumours.

The findings of our study reveal that UC does have a fair sensitivity of diagnosing HGUC. However in certain conditions like presence of excessive inflammation and reactive atypia, one is likely to miss reporting LGUC and other malignancies like SCC and small round cell neoplasms. However a positive correlation is noted in category 3, 4 and 5. Still we recommend that an elderly patient with hematuria and negative UC should further be investigated radiologically and clinically and a biopsy should be performed to rule out malignancy.

The Paris system has helped in increasing the diagnostic yield of high grade urothelial carcinoma. It also has the advantage of minimizing interobserver error and standardize the reporting format of UC. However we still feel it is important to consider presence of hematuria and correlation with cystoscopic findings while reporting cytology, especially with category '2' lesions. A repeat cytology in case of ND category should be considered. This would help in eliminating errors while reporting and build in more confidence of the surgeon in the report.

Conclusion

UC is the most cost effective and fairly reliable diagnostic modality for HGUC thereby helping in timely management of patients. However it has limitations of low sensitivity in diagnosis of LGUC and in follow-up cases.

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