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A Cytological and Histopathological Correlation of Urothelial Neoplasms with The Paris System

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Abstract

Introduction: Urothelial neoplasms once diagnosed need continuous follow-up, frequently via urinary cytology and cystoscopy. Urine cytology gives high sensitivity and specificity with high-grade urothelial carcinomas and low sensitivity and specificity with low-grade urothelial carcinomas. The Paris System was created to have fewer variable interobserver errors and more standardization of cytomorphological criteria. We aim to access the diagnostic efficacy of The Paris System to classify urothelial neoplasms by comparing histological and cytological correlation.

Material and method: 340 cases were searched retrospectively of urine cytology and histopathology in Sri Aurobindo Institute of Medical Sciences. Patients' age, sex, any other primary malignancy, smoking history, cystoscopy results, and one-year follow-up of patients having undergone surgery were included.

Result: Histological and cytological correlation was found in sixty-five percent of patients. Three percent were false negative and five percent were false positive in discordant results in which 14 percent were low-grade urothelial carcinoma. The sensitivity of urine cytology was 64 percent and specificity was 91 percent with a positive predictive value of 80 percent and negative predictive value of 82 percent.

Conclusion: The Paris System can improve the efficacy and accountability of predicting urine cytology for high-

grade urothelial carcinomas. Whereas, low-grade urothelial carcinomas require further investigations and workup along with urine cytology to improve patient care and early detection. Also, sample bias should be taken into consideration.

Keywords: Urinary Cytology, Primary Malignancy, Cytologic Diagnoses.

Introduction

Urine cytology is a routine checkup and plays a pivotal role in daily urological examination in patients with unexplained hematuria. It is a gold standard test for urothelial carcinoma when combined with cystoscopy [1]. The underlying clinical condition, type of specimen, and grading of urothelial carcinoma determine the sensitivity for urothelial carcinoma [2]. Urine cytology has been proven as highly specific and sensitive for high-grade urothelial carcinoma whereas has limited value in the diagnosis of low-grade urothelial carcinoma [3]. Equivocal and atypical results cause most of the problems and management ambiguities [4]. Urine cytology has been highly sensitive for detecting high-grade urothelial carcinoma which has a more aggressive course, and potential for metastasis and invasion. Whereas, its sensitivity for low-grade urothelial carcinoma is very low with high interobserver error [5]. To address this discrepancy, in 2016 The Paris System for Reporting Urinary Cytology (TPS) was proposed to create a standardized approach with specific diagnostic categories using defined cytomorphologic criteria [6].340 cases were searched retrospectively of urine cytology and histopathology in Sri Aurobindo Institute of Medical Sciences. Patients' age, sex, any other primary malignancy, smoking history, cystoscopy results, one year follow-up of patients having undergo neuro surgery were included.

Material And Method

Cytology: Urine specimens were prepared as ThinPrep slides. Since it's not a routine practice in our institute to prepare a cell block on urine cytology until a cell pellet is seen. Cell block preparation was not done in any of the cases of urine cytology. One surgical pathologist, one cytotechnician, three pathology residents, and two certified cytopathologist reviewed the cases in a blindfolded method without knowing about the surgical history of the patient. Criteria outlined in TPS were used to diagnose and cases were placed in the following categories: negative for high-grade urothelial carcinoma (NHGUC), atypical urothelial urothelialcells (AUC), suspicious for high-grade urothelial carcinoma (SHUC), and high-grade urothelial carcinoma (HGUC). Cytology of all cases was reviewed and consensus was achieved on discrepant diagnoses following group discussion. The positive predictive value, negative predictive value, sensitivity, specificity, and accuracy were calculated.

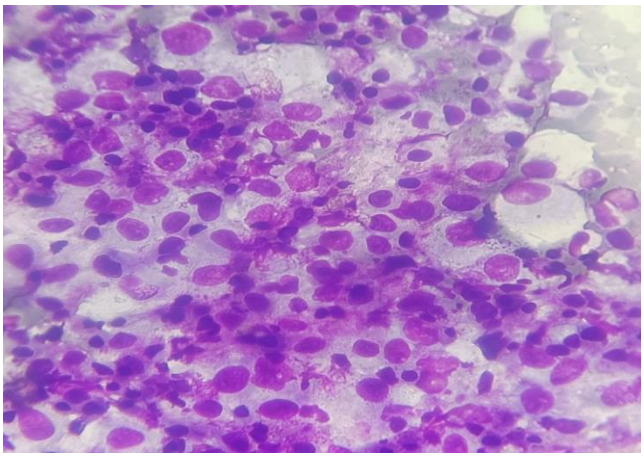

Figure 1: Urine cytology of High-Grade Urothelial Carcinoma showing urothelial cells with high N:C ratio (>0.7), moderate nuclear hyperchromasia, and irregular nuclear border

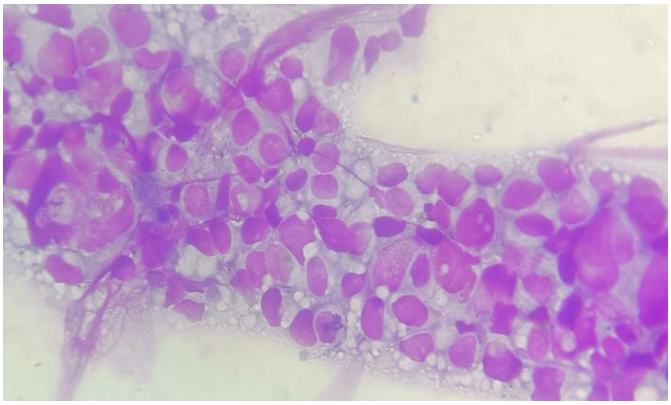

Figure 2: Urine cytology of High-Grade Urothelial Carcinoma showing urothelial cells with high N:C ratio (>0.7), highly pleomorphic cells, severe nuclear hyperchromasia, and irregular nuclear border.

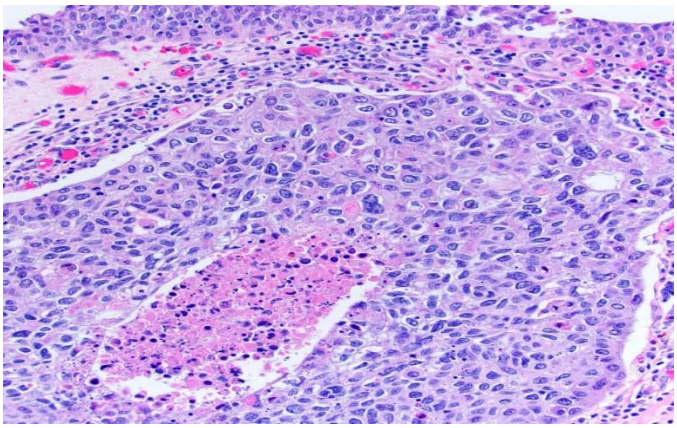

Figure3: showing histopathology slide 40 x of high grade urothelial carcinoma.

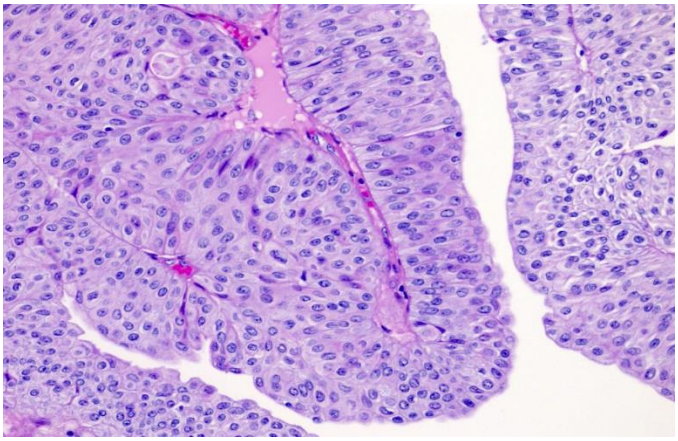

Figure 4: showing histopathology slide 40 x of low grade urothelial carcinoma.

Specimen adequacy: The criterion for specimen adequacy was utilized as previously demonstrated by Xing et al. [7]. A minimum of fifty well-preserved urothelial cells should be visualized to label a specimen as adequate. Specimens with urothelial cells of less than fifteen cells or being completely obscured by blood, lubricating gel, or inflammation were labeled as unsatisfactory. A few cases in the range of 15 to 49 urothelial cells were defined as less than optimal. In our study less than optimal were labeled as negative provided no atypical cells were seen.

Cytology histology correlation: Histological results are gold standard tests for follow-up cases and further patient management.

One-year follow-up cases were reviewed considering the cases of sampling bias that may occur in biopsy. Following the guidelines of Brimo et al. [8] we chose the highest-grade diagnosis of histology within one year from the studied sample date as the diagnosis. Cyto-histological diagnosis correlations were divided into concordant or discordant. A true positive case is defined as when cytology and its concurrent biopsy or follow-up biopsies are positive. For the positive cases of cytology whose concurrent histology is negative and came out to be positive after one year of follow-up, then that case is considered as true positive.

True negative is determined if both the cytology and histology of a patient are negative. False positive is when cytology diagnosis is atypical or higher and both biopsy and follow-up histology came out to be negative. Furthermore, a false negative is when cytological results are negative for malignancy and histopathological results come out to be malignant.

Result

Clinical data: Patients' age ranged from 18 to 95 years with a mean age of 68 years. A total of 156 patients were male patients (75%). Smokers were 61 percent and 35 % of patients never smoked. The smoking status of 12 patients (4 %) was unknown. The smoking status of the remaining patients was unknown (4%). Cystoscopy reports could be traced for 234 patients out of 340 patients. Out of these 144 patients (57 %) had erythema with or without irregular areas; 102 cases (41%) identified lesions or masses (papillary or raised or flat lesions) and 6 demonstrated no mucosal abnormalities (2%). Cystoscopic findings gave cordial results with high-grade urothelial carcinoma and low-grade urothelial carcinoma except in two cases in which no mucosal findings were found but high-grade urothelial carcinoma was diagnosed.

Cytologic diagnoses: The majority of urine samples collected were reported as negative for high-grade urothelial carcinoma, 206 cases (60%), were diagnosed as negative for urothelial carcinoma, 38(11%) were diagnosed as atypical, twelve cases (4%) as suspicious for high-grade urothelial carcinoma, and thirty cases (9%) were reported as high-grade urothelial carcinoma. Fifty–four cases (16%) were categorized as unsatisfactory by The Paris System. At the time of review, twenty-six cases (7%) were classified as less than optimal and were diagnosed as negative for high-grade urothelial carcinoma. 186 cases had cystoscopy results in a total of 206 cases which were reported negative for malignancy in urine cytology. 74 of these 186 cases (40%) had a specific lesion on cystoscopy. Of these 74 cases, 34 cases (46%) were negative for high-grade malignancy on histology, with 20 cases (27%) diagnosed with high-grade urothelial carcinoma on biopsy. 12 of the 32 cases called AUC (atypical urothelial cells) on cytology exhibited a targeted lesion on cystoscopy (38%), and 6 cases (50%) were negative 4 and cases (33%) were high-grade urothelial carcinoma on histology. All cases were labeled as suspicious for high-grade urothelial carcinoma or high-grade urothelial carcinomas on cytology were high-grade or low-grade histology, although only six cases and ten cases had a lesion identified on cystoscopy, respectively.

Cytologic and histologic correlation:

All cytology samples had at least two concurrent biopsy specimens for surgical pathology, of which 176 were diagnosed as benign (52%), 102 as high-grade urothelial carcinoma (30%), 48 cases as low-grade urothelial carcinoma (14%), and 14 atypical (4%). Cytologic histologic correlation was identified in 200 (59%) cases as true positive and true negative, constituting sixty cases (18%) and 140 (41%) cases, respectively. Discordant cases were diagnosed in 140 cases (41%). Evaluation of the corresponding diagnoses showed that of the 206 cases identified as negative on cytology, 144(70%) were labeled as benign, 30 (15%) was identified as low-grade urothelial carcinoma, 28(14%) were diagnosed as high-grade urothelial carcinoma, and 4 (2%) were diagnosed as atypical urothelial cells on histology. Of the 38 cases reported as atypical urothelial cells on cytology, the two concurrent biopsy specimens were identified as benign in 20 (53%) cases, high-grade urothelial carcinoma in 10 cases (26%), atypical urothelial cells in 6 cases (16%), and low-grade urothelial carcinoma in 2 cases (5%). Twelve cases were diagnosed as suspicious of high-grade urothelial carcinoma on histology. Of these, 8 (67%) were high-grade urothelial carcinoma on histology, Two cases (17%) were diagnosed as low-grade urothelial carcinoma and two cases were (17%) benign on histology. Thirty cases were diagnosed as positive for high-grade urothelial

carcinoma on cytology. Of these, twenty-four cases (80%) were concordant with histology as high-grade urothelial carcinoma, four cases (13%) were benign on histopathology, and two cases (7%) were diagnosed as low-grade on histology.

Discussion

Urothelial neoplasms usually present a wide range of prognoses and different spectrum of diseases. After the first diagnosis of histopathology, the patient is always at risk of developing new lesions or masses. For this very reason, follow-up of these cases is an inevitable part of management. Follow-up is mostly performed by urine cytology and cystoscopy. And these lesions are generally superficial; which can be managed via cystoscopy [9]. Urinary cytology is economical, accessible, and non-invasive for early diagnosis and surveillance of urothelial tumors; however, it can show wide interobserver variability. The Paris System is a specific classification system that provides basic criteria for cytomorphologic classification done for categorizing the cytology results. This plays an important role in patient follow-up and management [10]. Our study aimed to evaluate the cytologic criteria of The Paris System through the correlation of urinary cytology with concurrent histopathological findings to identify diagnostic efficacy and the limitations of the Paris System there is cyto-histologic discordance. Many studies have illustrated that the diagnostic accuracy, sensitivity as well as specificity were improved when the Paris system of urine cytology was used in comparison to a conventional reporting system of the institute [6,10-12]. Our study illustrated that negative predictive value of 79%, and similar prior studies have shown the negative predictive value to be variable ranging from 72%-98%, and directly proportional to a patient's prior history of high-grade urothelial carcinoma and the type of urine specimen [6,10,11,13,14]. Studies performed on inadequate urine samples showed that inadequacy is mainly due to a lower volume of voided urine. This is due to an operator's error. Catheter and instrumented samples give an adequate number of urothelial cells [15-17]. Prather et al described that a minimum count of twenty well-preserved and well-visualized urothelial cells per ten high power fields are required for catheterized samples and instrumented urine specimen adequacy with increased sensitivity in the identification of atypical and HGUC with increased cellularity[18]. Low-grade urothelial carcinomas are very difficult to diagnose in urine cytology with very low sensitivity and poor interobserver agreement [19-21]. The results of our study may be limited by the selection of the cases. Only cytology cases with concurrent histology were included, resulting in the majority of the specimens being bladder washes and very few voided urines. Therefore, the percentages of reported TPS categories do not represent all urine cytology specimens seen in our laboratory, as most patients do not undergo a follow-up biopsy. In conclusion, our results are supportive of TPS's ability to improve the reliability and accuracy of interpretations made in urine cytology, especially for high-grade lesions. In our experience, TPS provides standardized criteria, thus reducing interobserver variability and integrating cytopathologist thresholds. In addition, it reduces instances of pooling together any abnormal urines into an atypical category by including all reactive benign processes in the negative category. The Paris system for urinary cytology in the current study did fall short of detecting low-grade urothelial carcinoma lesions as it is rare to see papillary clusters with fibrovascular cores. Additional studies should be prioritized for low-grade urothelial neoplasms.

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