

Cytological Findings in Patients with Haematuria

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ABSTRACT:

BACKGROUND:

Regardless of the accessibility of more up to date and more modern methods of investigations, urinary cytology still remains the most regularly utilized non-invasive investigation for the diagnosis of cancer of the bladder.

OBJECTIVE:

To assess the helpfulness of urine cytology in assessment of patients with hematuria for the presence of malignancy.

PATIENTS AND METHODS:

A total of 1560 recently voided urine samples got at private clinics from patients with hematuria, whether gross or microscopic, over a time of three years were incorporated in the study. Physical and microscopical (cytological) examination done for all samples.

RESULTS:

Among these cases of hematuria incorporated in the study, 23.7% (370 cases) were found to have positive finding of atypical cells. In these cases with atypia, 48.7% (180 cases) were proved to have malignancy both with cystoscopic findings and the histopathological biopsy. The remaining cases of atypia were found to be reactive, either due to instrumentation or foreign body. In an extensive number of cases of hematuria, that is, 1190 cases (76.3%) no atypical cells were identified.

CONCLUSION:

Urine cytology can distinguish urothelial cells changes and high grade bladder tumor so it is a good tool particularly with coordinated effort amongst clinician and cytopathologist. Urine cytology can be utilized as an adjunct test in assessment of patients with hematuria.

KEYWORDS: atypical cells, bladder carcinoma, hematuria, urine cytology.

INTRODUCTION:

Haematuria is defined as the presence of the red blood cells in urine which is always ominous sign, and generally the patient makes a prompt visit to the physician. ⁽¹⁾ The Joint Consensus Statement on the initial Assessment of haematuria now terms macroscopic or gross haematuria as "visible" haematuria (VH)-the patient or doctor has seen blood in the urine or describes the urine as red or pink (or "cola-coloured-occasionally seen in acute glomerulonephritis). Microscopic or dipstick haematuria is "non-visible" haematuria (NVH). Non-visible haematuria is sorted as symptomatic (s-NVH, i.e. LUTS such as frequency, urgency, urethral pain on voiding, suprapubic pain) or asymptomatic (a-NAV). ⁽²⁾ Bladder cancer is the second most common genitourinary cancer. The occurrence is more in whites than blacks but when occurs in blacks they have poor prognosis. The mean age at presentation is 65 years and about 75% of bladder cancers are localized to the

bladder; while 25% have metastatic spread to regional lymph nodes or distant sites. ⁽³⁾

The most important risk factors for urothelial cancer are age and environmental toxins. So the incidence and prevalence rates rise with age, reaching the peak in the eighth decade of life, and strong association between urothelial cancer and environmental toxins exposure is observed. The incidence of urothelial cancer has been increasing over the last 60 to 70 years, but the rate of increment has recently decreased significantly and in some geographic areas has stopped. Unfortunately, the incidence rate is increasing being more rapid in underdeveloped countries where industrialization has resulted in more exposure to carcinogens. ⁽⁴⁾

The bladder cancer are mostly non-muscle invasive or muscle invasive transitional cell carcinoma (TCC) of low histological grade which have a better outcome when treated by transurethral resection or intravesical therapies. Nevertheless, still 23% to 35% of bladder carcinoma is of the high histological grade which

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would be muscle invasive or metastatic at the time of diagnosis.⁽⁵⁾ Survival for bladder cancer is strongly related to stage of the disease at diagnosis with one year survival rate of 95% for stage 1 decreasing to 35% for stage 4 in men and being of 91% for stage 1 decreasing to 27% in women.^(6,7) So, early detection and reliable diagnosis are very important in this group of population for a good outcome. The most popular analysis revealed that less than 10% of low-grade cancers are invasive, but as many as 80% of high-grade urothelial carcinomas are invasive.⁽⁸⁾ Despite several methods for screening and diagnosis of bladder cancer have risen of which urine cytology still remains the mainstay.⁽⁹⁾ Urine cytology is considered a straightforward, safe, and inexpensive test to diagnose hidden urothelial tumors. As most of the bladder cancers produce hematuria, even at non-invasive stages, screening of those at risk could provide a means of early detection, thus reducing cancer related morbidity and mortality.⁽¹⁰⁾

The sensitivity and accuracy of cytological examination are higher for urothelial carcinoma than for renal cell carcinoma, especially for the high-grade cancers.⁽¹¹⁾ The sensitivity of voided urine cytology for high-grade urothelial carcinoma was 94.2%, while it is controversial for low-grade urothelial carcinoma.⁽¹²⁾ Hence, we performed this study to assess the use of urinary cytology in cases of hematuria among routine voided urine samples.

PATIENTS AND METHODS:

This study was undertaken over a period of three years from March 2013 to October 2016 in two private clinics. During this period a total of 1560 recently voided urine samples selected from patients (both urologic and non-urologic) attending the outpatient services of our institution were included. The mean age of the hematuric

cases was 46 years (range 6 to 80 years) with 1210 males and 350 female cases.

Patients on anticoagulants, those with urinary tract infection, any type of trauma and those with proved malignant disease were excluded from this study

Around 50 mL of urine was collected in a clean container. The urine samples were usually the freshly voided morning sample, since sediments are best preserved in this specimen.

The processing of the samples was done in 2 parts:

1. Physical examination: Volume, color, appearance, odor.

2. Microscopic (cytologic) evaluation: Centrifugation of the urine sample at 800 rpm for 30 minutes was done, and the prepared slide stained by Papanicolaou stain. The presence of inflammatory cells, non inflammatory cells, and other cytological details as atypical cells – India ink cells, necrosis, nuclear-cytoplasmic (N/C) ratio, cytoplasmic details, hyperchromasia and chromatin abnormalities were noted.

RESULTS:

A total of 1560 cases of hematuria (either microscopic (>3 RBCs/hpf) (13) or gross hematuria) were incorporated in this study. The mean age of the hematuric cases was 46 years (range 6 to 80 years) with 1210 males and 350 female cases. These hematuria cases were further evaluated and the samples were processed for cytology. Based on the presence or absence of atypical cells (urothelial cells exhibiting a N/C ratio exceeding 50% were considered as atypical) on cytology, these cases were classified into two broad classes as: negative and atypia. Majority of the cases i.e. 1190 cases (76.3%) were negative for atypical cells (as shown in figure 1) whereas, 370 cases (23.7%) showed presence of atypical cells.

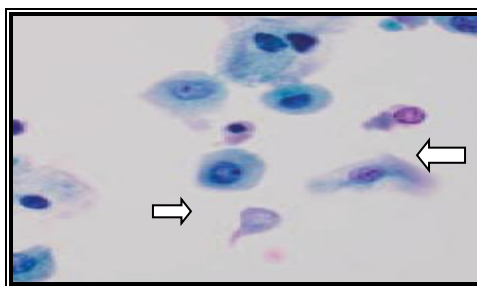


Figure 1: Normal urothelial cells. (PAP, 40X).

The cases under atypia were further reviewed and compared with histological biopsy and cystoscopy study data. After the review, 180 cases (48.7%) turned out to be malignant (true positive). The presence of high nuclear and cytoplasmic (N/C) ratio, nuclear pleomorphism, India ink cells (single cells with deep black

structureless nucleus) and chromatin abnormalities which are consistent features in the malignant atypical cells and correlated with histological findings of the tumor. [Figure 2](#) reveals tumor cells showing features of increased N/C ratio and hyperchromatic nucleus with irregular borders.

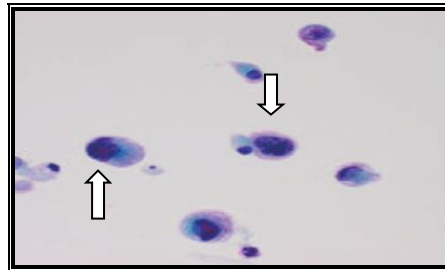


Figure 2: Discohesive urothelial cells of high grade transitional cell carcinoma.

instrumentation, calculi, crystalluria and indwelling catheter for long time. In the cases classified as negative, 640 cases (53.8%) showed signs of acute inflammation with presence of some reactive degenerated cells (Figure 3) and the remaining 545 cases (45.8%) showed presence of non-specific pathology without any contributory clinical, radiological and cystoscopy data.

These cells exhibit features of increased nuclear cytoplasmic ratio and hyperchromatic nucleus with irregular margins. (PAP, 100X)

20 cases (5.4%) with atypia were placed under category of suspicious of malignancy and later proved histologically to be cases of follicular cystitis. The remaining 170 cases of atypia (45.9%) were categorized as probably benign due to presence of predisposed history of

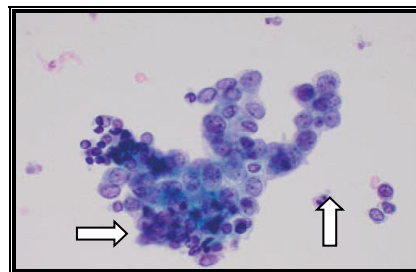


Figure 3: Reactive urothelial cells with few acute and chronic inflammatory cells.(PAP, 40X).

Five cases (0.4%) (false negative) had papillary growth on cystoscopic examination, thus the urine specimens were processed for cell block and found positive for malignant cells. These

cases were further confirmed to be transitional cell carcinoma on biopsy. In our study, sensitivity and specificity for urine cytology was 98.5% and 98.3% respectively.

Table 1: The number of cases according to the causes of hematuria.

Atypical cytology/ N 370			Negative cytology/N 1190	
Malignant/N 180	Benign/N 170	Suspicious/N 20	Acute inflammation/N 640	Non-contributory/N 545
	Indwelling catheter	Follicular cystitis	cystitis	Mild glomerular disease
	Instrumentation			
	Calculi			
	Intravesical therapy			
			Inflammation or infection of prostate	Infection (UTI,TB)
			calculi	Benign prostatic hyperplasia
			pyelonephritis	Calculi/crystals
				Trauma/instrumentation
				Anomalies of the kidney/urinary tract

DISCUSSION:

About 60% of bladder cancer present with haematuria, 10% of the patients with bladder cancer have asymptomatic microscopic hematuria and are positive for urine cytology.⁽¹⁴⁾ Thus the most important diagnostic tool of bladder cancer is combination of cystoscopy, biopsy and voided urine cytology. Among these, urine cytology is the non-invasive technique which is suitable for screening, diagnosis and follow-up.⁽¹⁵⁾ It can detect cases of carcinoma *in-situ*, low grade non invasive tumor, and also the most aggressive high grade and invasive neoplasm. Urine cytology is more accurate in high grade tumor.^(16,17) Also, the risk of recurrence is very low in patients with negative findings on urine cytology, while an aggressive tumor course is predicted by the presence of high-grade cytological findings.⁽¹⁸⁾ In addition to these, urine cytology is also a more valuable indicator of the presence of concurrent atypical urothelial cells, and may indicate the need for bladder wash or mucosal biopsies.⁽¹⁹⁾

In this study, we found that about 23.7% (370 out of 1560 cases) of hematuria patients were positive for atypia and 48.7% (180 out of 370) are true positive for malignant cells in urine cytology. These patients were later histologically proven to have malignancy of urothelial tract. An overall specificity of 98% was found for malignancy in this study. Although the specificity of urine cytology is high, still it is not sufficient for accurate diagnosis of bladder cancer depending on urine cytology alone. A positive urine cytology needs further evaluation and more investigation of the patient.⁽²⁰⁾

A variety of lesions can lead to exfoliation of transitional cells including stones, infection, post surgical/instrumentation trauma and inflammatory process. Thus, false positive diagnosis is higher in urinary cytology compared

to other cytodiagnostic techniques. In addition, transitional cells can have great difference in sizes, shape, nucleation and show nuclear and cytoplasmic degenerative changes that can be mistaken for malignancy.^(20,21) In this study, 170 cases (45.9%) had atypical cells of reactive origin. These are the cases of less consequence and should be correlated by clinical data and confirmed histologically. Thus, interpretation of urine cytology should always be used as an adjunct to clinical data along with other diagnostic tools.

Additionally, in this study 20 cases which were false positive, showed cellular atypia on urine cytology, however, were histologically proven to be follicular cystitis. These cases should be dealt with great caution, as there are documented evidences of presence of pleomorphic cells in urine samples of these cases.⁽²²⁾

As often quoted, urine cytology is difficult to understand, because of many cells with pleomorphism which have enlarged hyperchromatic nuclei with prominent nucleoli can be benign, whereas cancer cells can have nearly normal look. Thus, the number of false-negative diagnosis is higher in urinary cytological specimen and more of clinical consequence.

Regarding screening of the patients with hematuria, many clinical questions persist. Many times hematuria will be intermittent/microscopic, hence its detection itself is beset with multiple problems. Some studies have raised doubts about the use of urinary cytology in evaluation of hematuria.⁽²³⁾ According to American urological association (AUA) recommendations, urine cytology is reserved only for patients with risk for TCC.⁽²⁴⁾ Others consider it as a good tool for screening in middle-aged or elderly patients.⁽²⁵⁾ Because of its subjectivity and absence of

consistency in reporting, urinary cytology is considered less than a perfect tool, even among expert cytopathologists. All these inconsistencies can be eliminated if the clinicians and cytopathologists meet eye to eye and use a practical clinical approach.

CONCLUSION:

Urine cytology can distinguish urothelial cells changes and high grade bladder tumor so it is a good tool particularly with coordinated effort amongst clinician and cytopathologist. Urine cytology can be utilized as an adjunct test in assessment of patients with hematuria.

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