Utility of urine cytology in evaluating hematuria with sonographically suspected bladder lesion in patients older than 50 years

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Abstract

Purpose: Investigate the utility of urine cytology (UC) in patients older than 50 years with hematuria and sonographically suspected bladder lesion.

Patients and Methods: Between April 2010 and June 2012, 152 patients above 50 years suffering from hematuria were included in this study. In all patients, ultrasound revealed a lesion suspected to be bladder cancer. Voided urine specimens were taken from all patients and transported to Pathology laboratory and processed within 1-3 h. All patients have undergone a cystoscopy examination and biopsy was taken from any suspicious lesion. The cytological diagnosis was reported as one of three categories, positive or negative or suspicious for malignancy.

Results: One hundred thirty three (87.5%) patients in this study proved to have bladder carcinoma in histopathological examination. The sensitivity of UC was 53.4% and only five patients were suspicious. Percentage of positive cytology was highest among patients having gross hematuria (51.3%), posterior wall lesions (75%), papillonodular configuration (81.8%), invasive cancer (59.1%) and bilharzial affection (52.5%).

Conclusion: Hematuria in patients older than 50 years with sonographically suspected bladder lesion mandates cystoscopy and biopsy. UC does not add more significant information in this group of patients.

Key Words: Bladder cancer, hematuria, urine cytology

INTRODUCTION

One of common reasons for urological consultation is gross hematuria or symptomatic microscopic hematuria especially in patients older than 50 years. With the presence of sonographically suspected bladder lesion raising the index of suspicion for the presence of bladder carcinoma. In this situation, cystoscopy should be done to exclude the presence of carcinoma.

The usefulness of obtaining urine cytology (UC) continues to be debated.[1,2] Previous studies investigated the utility of UC in evaluating patients with hematuria who had either high or low risk of bladder carcinoma,[1,2,6] regardless of their radiological finding. UC is a useful test for adjusting a clinician’s index of suspicion for patients undergoing hematuria evaluation.[5]

In this study, we investigate the utility of UC in evaluating patients older than 50 years suffering from hematuria and having suspected bladder lesion by ultrasound.
PATIENTS AND METHODS

The local ethics committee approved the study. Between April 2010 and June 2012, patients suffering from gross hematuria or lower urinary tract symptoms associated with microscopic hematuria were included in this study. All included patients had bladder wall lesion during ultrasound examination. Hematuria was defined as 1 episode of gross hematuria or greater than 3 red blood cells per high power field on 2 of 3 properly collected urinalyses.[7] The patients were admitted and managed in the Oncology Unit of Urology Department at Assuit University, Egypt. Patients with age below 50 years, upper urinary tract disease, hematological disease and catheterized patients were excluded from the study.

Patients undergo a renal tract ultrasound scan, urine culture, serum analysis of renal function and prostate specific antigen (for men). The patients were instructed to void urine in a small container.

UC processing and examination
The voided urine specimens were transported to Pathology laboratory and processed within 1-3 h. The voided urine specimen was centrifuged for 10 min and the sediment was placed on two slides and each slide was smeared by another slide through application of one slide over the other with gentle rubbing in a quick horizontal motion that distributes the material in a thin film over both slides. Then, immediate immersion in 95% ethanol was done for at least 30 min and the two slides are stained with hematoxylin and eosin (H and E) and the other two slides by Papanicolaou stain. The cytological diagnosis was reported as one of the three categories, positive or negative or suspicious for malignancy.

N.B. The slides were already prepared by spreading of a thin film of egg albumin on the slides for better preservation.

Cystoscopic examination
The patients then underwent cystoscopic examination under spinal anesthesia after informed consent. The site of the lesion and its morphologic pattern was reported and a biopsy was taken from the lesion for histopathological examination. The morphologic patterns were reported as papillary when the major part of the tumor appeared as sessile or pedunculated finger-like processes or nodulo-papillary when appeared as cauliflower-like mass or nodules or nodular when the bladder wall was thickened by the tumor, which bulges slightly in the lumen or ulcerative when appeared as a malignant ulcer.

The tissue obtained by the cystoscopy was fixed in 10% formalin for 24 h. Five-micron thick sections were cut from paraffin blocks. Sections were stained with H and E then examined microscopically.

The results of UC were compared with the cystoscopic and histopathological pictures. Non-malignant patients had a minimum of 6-month follow-up (6-14 months).

RESULTS
The age of patients ranged from 50 to 88 with a mean age of 64 years. There were 133 males and 19 females. No correlation found between patients age and UC. Thirty-seven patients had lower urinary tract symptoms and proved to have microscopic hematuria by urine analysis and the remaining patients had gross hematuria. One hundred thirty three (87.5%) patients in this study proved to have bladder carcinoma in histopathological examination. Of them patients, 26 had low-grade papillary transitional cell carcinoma (TCC) [Figure 1a and b], 16 had...
high-grade papillary TCC [Figure 2a and b], 66 had high-grade non-papillary TCC [Figure 3a and b] and 22 had squamous cell carcinoma [Figure 4a and b]. The low-grade papillary TCC group included two patients with papillary urothelial neoplasm of low malignant potential due to few number of this grade. In 53 out of the 133 patients, the cancer associated with bilharzial ova on histopathological examination of their cystoscopic biopsy (40%). In 84 out of the 152 patients, the UC revealed evidence of heavy sepsis in the form of numerous neutrophils, bacilli, bare nuclei and degenerated cells. The sensitivity and specificity rates as regard secondary bacterial infection are presented in Table 1.

Figure 2a: Cytologic smears from a case of high grade papillary transitional cell carcinoma. Malignant urothelial cells are shed as individual cells as well as tissue fragments. Note the variability in nuclear chromatin and cell size, irregular nuclear membrane and the high N/C ratio, (H and E, x100)

Figure 2b: Higher magnification of histologic section from the same case of Figure 2a. The neoplastic cells are markedly pleomorphic and hyperchromatic and exhibit no orientation relative to basement membrane, (H and E, x40)

Figure 3a: Cytologic smears from a case of non-papillary high grade transitional cell carcinoma. Note the irregular nuclear membranes and the prominent nucleoli. (H and E, x100)

Figure 3b: Higher magnification of histologic section from the same case of Figure 3a, (H and E, x40)

Figure 4a: Cytologic smears from a case of squamous cell carcinoma. Note the severe pleomorphism and hyperchromatism of malignant squamous cells, (H and E, x100)

Figure 4b: Higher magnification of histologic section from the same case of Figure 4a, (H and E, x40)
The overall percentage of positive cytology was 44.1% (67 patients out of 152) and only five patients were suspicious. Sensitivity of UC was 53.4% and specificity was 94.7% in our study series.

As regard histopathological results, the percentage of positive cytology in case of TCC was 49.5% and in case of squamous cell carcinoma was 54.5%. TCC patients were sub grouped based on the grade and papillary configuration. The percentage of positive cytology for each is presented in Table 1.

As regard the invasiveness of the tumor, patients with muscle invasive tumor (≥pT2) have 59% positive UC and patients with tumor invading lamina propria (pT1) or non-invasive carcinoma (pTa) have 46% positive UC.

The nodulo-papillary configuration yielded highest percentage of positive cytology (81.8%) in comparison to other tumor configuration. The percentages of positive cytology for other tumor configurations are presented in Table 1.

As regard the relation between the results of UC and site of lesion, we found that posterior wall lesions yield highest percentage of positive cytology (75%) in comparison to other sites [Table 1].

Five samples were marked as suspicious for UC, one of them revealed absence of tumor. Absence of malignancy was revealed in 19 patients (12.5%) in spite of suspicious lesions in ultrasound examination. Positive predictive value for pelvic ultrasound in this series is 87.5%. Eight patients of them had mucosal folds during cystoscopic examination. Three patients had Bilharzial granuloma and rest of patients had bulging prostatic adenoma during cystoscopic examination. Transurethral resection of prostate and bilharzial granulomas was done for three patients with bulging prostatic adenoma and three patients with bilharzial granuloma at the same time of cystoscopy. Patients received antibilharzial, Alpha-blockers or urinary antiseptic according to each individual situation. Four patients lost follow-up and the rest of patients complete follow-up period without evidence of malignancy.

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### Table 1: Association between the yield of UC and different tumor and patients characteristics

| Tumor and patients characteristics | Cytological diagnosis | Sensitivity | Specificity | P value |
|-----------------------------------|-----------------------|-------------|-------------|---------|
|                                   | Negative count (%)    | Positive count (%) | Suspicious count (%) |         |
| Hematuria                         |                       |              |             |         |
| Gross                             | 54 (47.0)             | 59 (51.3)    | 2 (1.7)     | 59.2    | 100     | 0.003   |
| Microscopic                       | 26 (70.3)             | 8 (21.6)     | 3 (8.1)     | 33.3    | 85.7    |         |
| Pathological diagnosis            |                       |              |             |         |
| Negative for tumors               | 18 (94.7)             | 0 (0.0)      | 1 (5.3)     |         |         | 0.000   |
| Low grade papillary TCC           | 4 (51.4)              | 22 (84.6)    | 0 (0.0)     |         |         |         |
| High grade papillary TCC          | 6 (37.5)              | 10 (62.5)    | 0 (0.0)     |         |         |         |
| High grade TCC                   | 44 (63.6)             | 22 (33.3)    | 1 (3.0)     |         |         |         |
| Squamous cell carcinoma           | 8 (36.4)              | 12 (54.5)    | 2 (9.1)     |         |         |         |
| UC                                | 2 (66.7)              | 1 (33.3)     | 0 (0.0)     |         |         |         |
| Invasion                          |                       |              |             |         |
| Non-invasive                      | 4 (26.7)              | 6 (73.3)     | 0 (0.0)     |         |         | 0.000   |
| Invasive (L.P)                    | 20 (54.1)             | 15 (40.5)    | 4 (5.4)     |         |         |         |
| Invasive (ms)                     | 18 (40.9)             | 26 (59.1)    | 0 (0.0)     |         |         |         |
| Cystoscopic picture               |                       |              |             |         |
| Papillary                         | 16 (40.0)             | 24 (60.0)    | 0 (0.0)     |         |         | 0.000   |
| Nodular                           | 36 (58.1)             | 24 (38.7)    | 2 (3.2)     |         |         |         |
| Papillo-nodular                   | 4 (18.2)              | 18 (81.8)    | 0 (0.0)     |         |         |         |
| Ulceration                        | 4 (66.7)              | 0 (0.0)      | 2 (33.3)    |         |         |         |
| Hemorrhagic area                  | 2 (66.7)              | 1 (33.7)     | 0 (0.0)     |         |         |         |
| Site of the lesion                |                       |              |             |         |
| Posterior wall                    | 6 (25.0)              | 18 (75.0)    | 0 (0.0)     |         |         | 0.000   |
| Lateral wall                      | 16 (42.1)             | 20 (52.6)    | 2 (5.3)     |         |         |         |
| Anterior wall                     | 24 (85.7)             | 2 (7.1)      | 2 (7.1)     |         |         |         |
| Bladder neck                      | 8 (61.5)              | 5 (38.5)     | 0 (0.0)     |         |         |         |
| Dome                              | 8 (26.7)              | 22 (73.3)    | 0 (0.0)     |         |         |         |
| Secondary infection               |                       |              |             |         |
| No                                | 30 (44.1)             | 36 (52.9)    | 2 (2.9)     | 63.3    | 100     | 0.140   |
| Yes                               | 50 (59.5)             | 31 (36.9)    | 3 (3.6)     | 45.2    | 90.9    |         |
| Bilharzias                        |                       |              |             |         |
| No                                | 54 (58.1)             | 36 (38.7)    | 3 (3.2)     | 47.5    | 93.3    | 0.233   |
| Yes                               | 26 (44.1)             | 31 (52.5)    | 2 (3.4)     | 62.3    | 100     |         |
| Sex                               |                       |              |             |         |
| Male                              | 67 (50.4)             | 61 (45.9)    | 5 (3.8)     | 55.6    | 93.7    | 0.285   |
| Female                            | 13 (65.4)             | 6 (31.6)     | 0 (0.0)     | 37.5    | 100     |         |

UC: Urine cytology, TCC: Transitional cell carcinoma, CIS: Carcinoma in situ, L.P: Lamina propria
DISCUSSION

Cystoscopy and biopsy is the gold standard for detection of urothelial carcinoma of the urinary bladder but it is invasive and causes significant patient discomfort. Urinary cytology is a non-invasive method for detection of urothelial carcinoma of the urinary bladder. Nowadays, ultrasonography has come to be the mainstay in investigating urinary tract pathology and for the Urologist it is considered a bedside test.

Value of voided UC in evaluating patients with hematuria will vary according to the level of associated tumor risk. In low risk patients, UC added a significant cost without additional diagnostic benefit, while in high risk patients it is a useful test. Patients older than 50 years with hematuria and bladder lesion by ultrasound are considered highly risky for the presence of urothelial carcinoma.

In our study, there were 57 cases with positive UC out of 133 cases proved to have bladder cancer; this means that the sensitivity of UC in diagnosis of bladder cancer in the selected patients was 53.4%. It might be noteworthy that the sensitivity of UC reported by most of the previous studies was more or less within the range of our results [Table 2]. However, Barlandas-Rendón et al., and García Castro et al., reported higher percentage of sensitivity of UC. It seems that the factors behind this variability are multifactorial; it might depend upon the type of bladder carcinoma, grade, stage, the presence or absence of secondary infection and difference in technical aspects. Also, the association with bilharziasis might be a factor.

In this study, the sensitivity of UC was better in those patients who had gross hematuria. This correlates with the results of Viswanath et al., study in which out of 100 patients presented with gross hematuria and proved to have malignancy by cystoscopic biopsy, 65 patients had positive UC (65%) while out of 17 patients presented with microscopic hematuria and proved to have malignancy by the cystoscopic biopsy, 9 patients had positive UC (52.9%). These observations emphasize that the sensitivity of UC is better in those patients with gross hematuria.

The yield of UC in our study was better in nodulo-papillary lesions followed-by papillary lesions then nodular lesions. This agree with a study of Elwi et al., who stated that fungating tumors give the best chance for exfoliation of cells and hence for cytological diagnosis and on the contrary, the malignant ulcers exfoliate necrotic cells, which may be unsatisfactory for the cytological diagnosis.

As regard the relation between histopathological result and UC, other studies reported more sensitivity of UC in high-grade TCC cases as compared with low-grade TCC cases. However, the relatively low sensitivity of UC in high grade TCC in our study may be explained by heavy secondary urinary sepsis and the degenerative and necrotic changes that have been frequently detected in cancer of bilharzial bladder. In fact, the urinary sepsis and the degenerative changes that were detected in the exfoliated tumor cells markedly masked and interfered with the positive cytological diagnosis. However, Secondary bacterial infection per se does not significantly affect the yield of UC in this study.

Johnson stated that the squamous cell carcinoma can be easily diagnosed cytologically as the cells are always present in groups. Pedamallu and Alexandrou states that higher staging (pT2: 72%) was positively associated with malignant cytology than lower staging (pTa: 19%). These are in collaboration with our study that obtained slightly more positive UC in squamous cell carcinoma than that of the TCC (54.5% vs. 50.4%) and more positive UC in advanced stages (59% for muscle invasive carcinoma versus 46% for lamina propria and non-invasive carcinoma).

Abd El Gawad et al., reported that the sensitivity of UC for bilharzial bladder cancer was 69.6% while that of non-bilharzial bladder cancer was 39.1%. These results are in corporation with our results in which sensitivity of UC was 62.3% in bilharzial bladder compared with 47.5% for non-bilharzial.

Relation of UC to site of tumor was not taken in consideration in the previous studies; however, in this study, the exfoliation of malignant cells in urine was more when the lesion involving the posterior wall followed by multicentric lesions, then lesion involving the lateral wall.

The accuracy of pelvic ultrasound in detecting of bladder carcinoma was studied previously with positive predictive value ranged from 91% to 94% depending on the accuracy of

| Table 2: Comparison between the sensitivity of UC in different studies | Author | No. of cases | Sensitivity of UC % |
|---|---|---|---|
| Present study | 152 | 53.4 |
| Raitanen, 2000 | 151 | 30.3 |
| Chautard, 2000 | 106 | 46.7 |
| Barlandas-Rendón, 2002 | 115 | 76.1 |
| Shoshatri, 2005 | 54 | 48.4 |
| Hasan, 2007 | 30 | 44 |
| Garcia Castro, 2008 | 109 | 97 |
| Blick, 2012 | 778 | 38 |
| Hoseini, 2012 | 144 | 44.2 |
| Total and means | 1537 | 52.1 |

UC: Urine cytology
modern ultrasonography machines. Our results have less positive predictive value and this may be attributed to use of old machine in this study.

The point of weakness is that the results of this study cannot be extrapolated to the general population because all of our patients had an established need for undergoing cystoscopy.

CONCLUSION

Hematuria in patients older than 50 years with sonographically suspected bladder lesion mandates cystoscopy and biopsy. UC does not add more information; however, its sensitivity increased when there are gross hematuria, posterior wall lesion, nodulo-papillary configuration, invasive cancer and bilharzial affection.

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