Original Article

The influence of urine cytology on our practice

Mahmoud Alameddine, Anmar Nassir[1]

International Medical Center, Jeddah, [1]Umm Al-Qura University, Faculty of Medicine, Makkah, Saudi Arabia

Abstract

Objective: Bladder cancer is a common malignancy. It is ranked ninth among male population in Saudi Arabia. Urine cytology is used by some physicians routinely in the workup for diagnosis and follow-up of patients with urothelial cancer. Our objective is to determine whether urine cytology is still essential in the work up of suspected urothelial cancer patients and to measure its cost-effectiveness.

Materials and Methods: We reviewed all urine cytology reports that were performed over a period of five years from 2006 to 2010 in the International Medical Center in Jeddah, Saudi Arabia. The medical records of patients with cytology reports of both positive for malignant cells and atypical cells suspicious of malignancy were retrospectively, studied for age, sex, nationality, cystoscopic findings, imaging results, and total cost.

Results: A total of 563 urine cytology tests were done on 516 patients. Two patients were positive for malignant cell and 10 showed atypical cells suspicious of malignancy. All 12 patients underwent imaging and/or cystoscopy as part of their complete work up for hematuria. The two patients with positive cytology had a cystoscopic confirmation of bladder tumor. In the 10 patients with atypical cells, bladder tumor was identified in seven using cystoscopy and/or imaging. The mean age was 54.6±16 year (range 15-95). The total cost was 140,750 SR (37,533 USD) for a yield of 0.3% positive results and 2% atypical cytology.

Conclusion: Routine urine cytology did not affect the diagnostic strategy for urothelial cancer. It should be only used in selected patients.

Key Words: Hematuria, transitional cell carcinoma, urine cytology, urine markers, urothelial cancer

Address for correspondence:
Dr. Mahmoud Alameddine, International Medical Center, PO Box 2172, Jeddah 21451, Saudi Arabia. E-mail: dralameddine@hotmail.com
Received: 01.06.2011, **Accepted:** 28.07.2011

INTRODUCTION

Bladder cancer is a common malignancy. In Saudi Arabia, this cancer is ranked ninth among male population and twenty second among female population with a male to female ratio of 4.4:1.[1] In the United States, it is the fourth most common cancer among men after prostate, lung, and colorectal cancer. It is nearly three times more common in men than in women, accounting for 6.6% and 2.4% of all cancer cases in men and women, respectively.[2] Cigarette smoking is the most common risk factor and doubles the risk of bladder cancer, accounting for approximately 50% of the bladder cancer deaths in men and 30% in women.[3] More than 90% of bladder cancers are urothelial carcinoma (UC) which shows an increased number of endothelial cell layers with papillary foldings of the mucosa, loss of cell polarity, abnormal cell maturation from basal to superficial layers, increased nuclear-cytoplasmic ratio, prominent nucleoli, clumping of chromatin, and increased number of mitoses.[4] There are several grading systems, but probably the most widely used is that adopted by the World Health Organization (WHO). Recently, many investigations have been developed to detect early urinary tract malignancy which includes various imaging modalities, multiple urine markers and cystoscopy. For many years urine cytology has been used to diagnose and follow patients with UC. It was first reported by Papanicolaou and Marshall in 1945.[5] However,

Access this article online

Quick Response Code:

Website: www.urologyannals.com

DOI: 10.4103/0974-7796.95550

the presence of exfoliated neoplastic cells was described by Sanders as early as in 1864.[6,7] Urine cytology has been requested by urologists and non-urologists for patients with a history of UC and patients at higher risk for bladder cancer due to different factors such as history of smoking or symptoms including hematuria, irritative symptoms, and dysuria.[8] The American Urology Association (AUA) best practice policy recommended voided urine cytology in all patients with asymptomatic hematuria who belong to higher risk group and it is a first line option in those who belong to low risk group.[9] Having cystoscopy and urothelial biopsy as the gold standard for detecting bladder cancer in the era of advanced imaging technology, we reviewed all urine cytology results done in our institution in order to determine whether urine cytology is still essential in the work up of suspected UC patients and to measure its cost-effectiveness.

MATERIALS AND METHODS

We retrieved all the urine cytology reports for both voided urine and bladder wash samples that were performed over a period of five years from 2006 to 2010 at the International Medical Center (IMC) in Jeddah, Saudi Arabia. Urine cytology was ordered by urologists and non-urologists for patients with hematuria (gross or microscopic), persistent irritative symptoms, for high risk group (age>40 years, smoker, exposed to chemicals, analgesics abuse), for follow-up of patients with history of UC and when cystoscopy is equivocal for cancer. Almost all the results of urine cytology fell into one of the following categories: No malignant cells, atypical/no definite malignant cells, atypical/suspicious of malignant cells, and malignant cells. We, retrospectively, reviewed the medical records of patients with cytology results of both positive for malignant cells and atypical cells/suspicious of malignancy in terms of age, sex, nationality, cystoscopic findings, imaging results, and total cost. Radiological imaging includes ultrasound of kidneys and bladder, intravenous pyelography, CT scan of abdomen and pelvis, and MRI of abdomen and pelvis. During cystoscopy, any suspicious erythematous mucosal areas were biopsied and any papillary tumor was resected and sent to the histopathology lab. If any imaging modality suspected pelvi-ureteric mass, brush biopsy was taken.

RESULTS

A total of 563 urine cytology tests were done on 516 patients, 360 males, and 156 females with average age of 54.6 ± 16 years (range 15-95). There were 392 (76.1%) Saudies, 123 (23.8%) non-Saudis including 68 Middle Easterns, 32 Africans, 14 Asians, 7 North Americans, 3 Europeans. Two patients were positive for UC, one with a high grade and the other with a low grade [Table 1]. Consequently, histopathology reports correlates with the cytology results. In addition to the bladder UC, one patient showed concomitant renal pelvis UC. Ten patients showed atypical cells/suspicious of malignancy [Table 2]. Among this group, bladder tumor was identified in seven (70%) using cystoscopy and/or radiological imaging. Of the 10 patients, 8 underwent cystoscopy. Five of them turned out to have bladder tumor and subsequently UC. In the other two, no histological records were identified but radiological imaging revealed obvious bladder tumor. They were informed about their findings and continued their management in other hospitals. The mean age of the atypical cells/suspicious of malignancy group was 60.8 years (range: 32-84). The total cost of 563 urine cytology tests was 140,750 Saudi Riyal (USD 37,533) for a yield of 0.3% positive results and 2% atypical cytology.

DISCUSSION

Urine cytology is a microscopic evaluation of morphologic features of shed urothelial cells. Results vary from malignant cells to atypia, low or acellular specimen, inflammation or degenerative changes. A fresh, uncontaminated specimen is required in order to maximize the evaluation.[10] Malignant cells identified in cytological specimens may come from either low grade or high grade lesions. Cells designated as low grade should correlate with histological grade 1 lesions and some histological grade 2 lesions. Cells designated as high-grade correlate with some grade 2 lesions, all grade 3 lesions and UC *in situ*.[11]

Atypical category remains a wastebasket that includes both specimens that are suspicious of malignancy and specimens without this possibility as well as specimens that enclose cell clusters or poorly preserved cells.[12] There is no consensus regarding the terminology and diagnostic criteria that should be used for urothelial atypia.[13] In an attempt to standardize the diagnostic categories for urine cytology, the Papanicolaou Society of Cytopathology recommended in 2004 a diagnostic scheme that included an "atypical urothelial cells" category. The Society also suggested classifying the atypia as reactive or neoplastic.[14] Some authors showed that despite the fact that an atypical unclear (if neoplastic or reactive) diagnosis has a higher rate of detection of high-grade cancer on follow-up biopsy in comparison with an atypical favor a reactive process or a

Table 1: Urine cytology positive for malignant cells

Urine cytology	Age	Sex	Nationality	Imaging	Cystoscopy	Final diagnosis
High grade TCC	71	F	Sudanese	CT: Bladder mass	Bladder tumor	Bladder high grade TCC
Low grade TCC	63	F	Saudi Arabian	CT: Right renal pelvis mass	Bladder tumor	Bladder and right renal pelvis low grade TCC

negative diagnosis (45% vs 29% and 15.5%, respectively), this difference remains statistically insignificant and recommended conservative approach[15]

The specificity and sensitivity of urine cytology has been studied tremendously. A general concept is built regarding its low sensitivity and high specificity which varies widely around 15 to 90% for sensitivity and 80 to 100% for specificity.[16,17] False positive results occur secondary to instrumentation, inflammation, infection, stones, treatment with chemo and radiotherapy.[15] It has been noted that the sensitivity is related to tumor grading. Unfortunately, this test lacks sensitivity for small tumors, low and intermediate grade tumors which constitutes the majority of UC. This is secondary to the fact that small tumors, low grade tumors, or both are less likely to exfoliate cells spontaneously because the strong attachments among cells are better preserved, and the degree of morphological departure from normal is less, making recognition difficult.[18] As a result, negative cytology cannot rule out UC and further radiological imaging and/or cystoscopy are warranted. Moreover, all positive results as well as atypical/suspicious of malignancy needs cystoscopy to confirm the diagnosis. Hence, the role of urine cytology in UC management is questionable. Despite the limitations, urine cytology remains very useful in the follow-up of patients with high grade UC where sensitivity and specificity reach 90%.[19] Several techniques are being adopted to improve the sensitivity yield of urine cytology. The use of the whole voided specimen for centrifugation and multiple urine samples (three samples) increase the sensitivity from 43.9% to 56.1% and 66.7%, respectively.[20] However, it significantly increases cost and patient compliance is difficult. It has been shown that bladder wash specimens provide more epithelial cells for examination than does voided urine.[21] Yet it is invasive and specimens which are acquired from flexible cystoscopy are proved to contain much less epithelial cells than that of rigid cystoscopy. As urine cytology is not a laboratory test. It requires visual evaluation of morphological changes and the interpretation of cytology is pathologist-dependent. It relies mostly on the level of the pathologist expertise and it lacks standard methods for reporting. Another factor that alters the sensitivity of urine cytology is the indication of urine cytology request. One study showed that there is a significant difference between the positivity rate amongst urologist and non-urologists request (56% and 6%, respectively).

Thus to enhance the cytology sensitivity, it should be limited to proper clinical situation.[22] In the face of those mentioned cytology limitations, scientists have developed numerous urinary markers to replace or combine urine cytology. These markers can detect tumor-associated antigens, blood group antigens, growth factors, cell apoptosis, nuclear matrix proteins, and nuclear aneuploidy. Different tumor markers are summarized in [Table 3].[11] In a comprehensive literature

Table 2: Urine cytology atypical cells/suspicious of malignancy

Age	Sex	Nationality	Imaging	Cystoscopy	Final diagnosis
32	M	Saudi Arabian	CT: No masses	Normal bladder mucosa	No abnormality
41	F	Pakistani	US: Thickening of bladder wall	Bladder tumor	Bladder low grade TCC
45	M	Egyptian	US: Bladder mass	Bladder tumor	Bladder low grade TCC
55	M	Saudi Arabian	US: No masses	Bladder tumor	Bladder low grade TCC
59	M	Saudi Arabian	CT: No masses	Normal bladder mucosa	No abnormality
60	F	Saudi Arabian	CT: Right renal pelvis mass	Normal bladder mucosa	Renal tissue with focal tubular degeneration
69	M	Palestinian	US: Bladder mass	Loss of follow up	-
73	M	Yemeni	MRI: Bladder mass	Bladder tumor	Bladder high grade TCC
78	M	Saudi Arabian	CT: Bladder mass	Loss of follow up	-
84	M	Saudi Arabian	CT: No masses	Bladder tumor	Bladder low grade TCC

Table 3: Tumor markers

Tests	Detects	Sensitivity (%)	Drawbacks
Bard BTA	Lysed basement membrane component	29 to 40	Low detection of grade I TCC Poorer predictive value than urine cytology
BTA stat	Human complement factor H-related protein	67 to 87	High false-positive with gross hematuria, prostate cancer, BCG
BTA TRAK	Human complement factor H-related protein	72	High false-positive with UTI, stones, instrumentation
NMP22	Nuclear matrix proteins	66	High false-positive with gross hematuria
Telomerase	Telomerase activity	70	False-negatives with gross hematuria False-positives with inflammation Complicated assay not widely available
Hyaluronic acid	Hyaluronic acid	92	Too early to substantiate results
Hyaluronidase	Hyaluronidase activity	100	No detection of grade 1 TCC
AuraTek FDP	FibrinogenFibrin/ fibrinogen degradation products	48 to 68	High false positive with gross hematuria
ImmunoCyt	Carcinoembryonic antigen and two bladder mucins	39 to 100	interpretation is complex and operator dependent
UroVysion	Certain chromosomal foci	73 to 81	

review and meta-analyses, it was reported that all urinary bladder markers have better sensitivity compared with cytology, especially for low grade disease, but do not match cytology regarding specificity.[17]

A recent study reviewed 2,568 cytology results. Twenty five patients (1%) were reported to have positive results for malignant cells with a total cost of EUR 250,000. Consequently, they concluded that urine cytology is not cost effective as an initial work up in patients with suspected UC.[7] In our institution, SR 140,750 (USD 37,533) was spent for a yield of 0.3% positive results and 2% atypical cytology.

CONCLUSION

Due to multiple limitations of urine cytology, with high financial burden, inability to exclude or confirm malignancy and further investigations are warranted no matter what is the result, urine cytology should not be used routinely. It did not affect the diagnostic strategy for suspected UC. Having the fact that ideal marker should be rapid, inexpensive and non-invasive with high sensitivity and specificity, researcher should continue searching for that marker.

REFERENCES

1. Cancer Incidence Report Saudi Arabia 2005. Available from: http://www.scr.org.sa/reports/SCR2005.pdf [Last accessed on 2011 May 18].
2. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, *et al*. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10-30.
3. National Cancer Institute. General information about bladder cancer. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/bladder/patient. [Last Accessed on 2005 Jan 11].
4. Koss LG. Tumors of the urinary bladder. Atlas of Tumor Pathology, second series, Washington, DC: Armed Forces Institute of Pathology; 1975:1
5. Papanicolaou GN, Marshall VF. Urine sediment smears as a diagnostic procedure in cancers of the urinary tract. Science 1945;101:519-20.
6. Sanders WR. Cancer of the bladder. Fragments forming urethral plugs discharged in the urine: Concentric colloid bodies. Edinb J Med 1864;10:273-4.
7. Falebita OA, Lee G, Sweeney P. Urine cytology in the evaluation of urological malignancy revisited: Is it necessary? Urol Int 2010;84:45-9.
8. Grossman HB, Messing E, Soloway M, Tomera K, Katz G, Berger Y, *et al*. Detection of bladder cancer using a point-of-care proteomic assay. JAMA 2005;293:810-6.
9. Grossfeld GD, Wolf JS, Litwin MS, Hricak H, Shuler CL, Agerter DC, *et al*. Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association best practice policy recommendations. Am Fam Physician 2001;63:1145-54.
10. Viswanath S, Zelhof B, Ho E, Sethia K, Mills R. Is routine urine cytology useful in the haematuria clinic? Ann R Coll Surg Engl 2008;90:153-5.
11. Brown FM. Urine cytology: Is it still the gold standard for screening? Urol Clin North Am 2000;27:25-37.
12. Renshaw AA. Subclassifying atypical urinary cytology specimens. Cancer 2000;90:222-9.
13. Deshpande V, McKee GT. Analysis of atypical urine cytology in a tertiary care center. Cancer 2005; 105:468-75.
14. Layfield LJ, Elsheikh TM, Fili A, Nayar R, Shidham V. Review of the state of the art and recommendations of the Papanicolaou Society of Cytopathology for urinary cytology procedures and reporting: The Papanicolaou Society of Cytopathology Practice Guidelines Task Force. Diagn Cytopathol 2004;30:24-30.
15. Brimo F, Vollmer RT, Case B, Aprikian A, Kassouf W, Auger M. Accuracy of urine cytology and the significance of an atypical category. Am J Clin Pathol 2009;132:785-93.
16. Liou LS. Urothelial cancer biomarkers for detection and surveillance. Urology 2006;67 Supplement 1:25-33.
17. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: Results of a comprehensive literature review and meta-analyses. Urology 2003;61:109-18.
18. Farrow GM. Urine cytology in the detection of bladder cancer: A critical approach. J Occup Med 1990;32:817-21.
19. Soloway MS. International consultation on bladder tumors. Urology 2005;66:20-1,40-1.
20. Planz B, Jochims E, Deix T, Caspers HP, Jakse G, Boecking A. The role of urinary cytology for detection of bladder cancer. Eure J Surg Oncol 2005;31:304-8.
21. Trott PA, Edwards L. Comparison of bladder washings and urine cytology in the diagnosis of bladder cancer. J Urol 1973;110:664-6.
22. Nabi G, Greene DR, O'Donnell M. How Important is Urinary Cytology in the Diagnosis of Urological Malignancies? Eur Urol 2003:43:632-6.

How to cite this article: Alameddine M, Nassir A. The influence of urine cytology on our practice. Urol Ann 2012;4:80-3.

Source of Support: Nil, **Conflict of Interest:** None.