ANALYSIS OF URINE CYTOLOGY AT A COMMUNITY HOSPITAL

Ibrahim Mansoor

Department of Pathology, St. John Hospital and Medical Center, Detroit.

Background: To review the pattern of urine cytology in our setting of a community hospital with age and gender distribution. Also to discuss the importance of this safe and inexpensive tool for diagnosing and screening urothelial cancers. We desire to encourage more wider and confident use of urine cytology in the routine practice. **Method:** We reviewed all the consecutive urine cytology specimens received at our institution during time frame of one year. The cytological diagnosis were grouped in four categories; 1: negative, benign or reactive cases; 2: cases showing acute inflammatory changes; 3: inconclusive cases and 4: malignant cases. Only the positive malignant cases were followed histologically to determine the accuracy and efficiency of urine cytological examination for positive cases. **Results:** A total of 1957 consecutive urine cytology specimens were reviewed. Majority of the cases were negative for tumour (67.19%). The most common diagnostic category was acute inflammatory case (17.3%) while inconclusive cases constituted 11.39% of total. There were 23 (1.18%) positive cases that were diagnosed malignant on urine cytology. These 23 malignant cases were followed histologically and 22 (95.6%) cases turned out to be malignant. **Conclusion:** Urine cytological examination is an efficient tool that has a good diagnostic yield in detecting malignant urothelial lesions. It should be used routinely for diagnosing, screening and for follow-up of all malignant urothelial lesions.

Keywords: Urine cytology, urothelial neoplasm.

INTRODUCTION

The urinary tract is lined by transitional epithelium and historically this epithelium was so named by Friedrich Henle, a 19th century German pathologist, because he thought that the urinary epithelium was 'transitional' between squamous and glandular[1,2]. It is now recognized as a specific type in its own right. Therefore, it is also called as 'urothelium'. However, it is interesting that some tumours of the transitional epithelium do indeed express the ability to differentiate along squamous or glandular lines and that patches of squamous and glandular mucosa are commonly interspersed in benign transitional epithelium. Urine cytology is useful in diagnosing diseases that involve this mucosal surface and the urinary collecting system lined by transitional epithelium. There are three basic types of exfoliated urinary tract specimens: (1) voided urine, (2) catheterized urine, and (3) brushing/washing specimens. These specimens should be processed immediately or refrigerated and processed as soon as possible. If a delay is anticipated, immediate fixation with 50% ethanol may preserve the specimen for several days. In the cytology laboratory the 'urinary fluid' is treated as other body fluids and is centrifuged. The processed specimen is used to prepare smears.

Cytologic examination of a urine specimen is a simple, safe, and inexpensive method that may uncover a hidden urothelial cancer[1,2]. Tumours of the urinary tract are relatively inaccessible to direct biopsy, and the tumours are often multifocal. Since the entire mucosal surface, including the farthest reaches of the urinary tract, is bathed in this easily obtained fluid, in theory, urine is the perfect specimen to examine for evidence of tumour. The well known indications for urine cytology examination are 1: for tumour detection and diagnosis of aggressive neoplasms or their follow-up, carcinoma *in situ*, small or inaccessible lesion as in ureters, pelvis, diverticuli etc.; 2: for screening of high-risk asymptomatic patients, as with industrial chemical or metal exposure, those with schistosomiasis or smokers etc.; 3: monitor tumours and therapy, for example low-grade non-invasive tumours, carcinoma in-situ[2]. Cytology may become positive long before the cystoscopy or biopsy. But lesions cannot be anatomically localized with urine cytology alone.

This study is an attempt to review the practice of urine cytology examination in our setting of community hospital. The importance of urine cytology as a simple, safe, and inexpensive method for diagnosing and screening malignant lesions is also discussed.

MATERIAL AND METHODS

Our study sample consisted of 1957 consecutive urine cytology specimens examined at Department of Pathology at St. John Hospital and Medical Centre, Detroit. Cases during the time frame of one year from August 2001 to September 2002 were retrieved from laboratory archives. The cytological diagnosis were grouped in four

categories according to WHO/ISUP (International Society of Uropathology 99)[3]; 1: negative, benign or reactive cases; 2: cases showing acute inflammatory changes; 3: inconclusive cases and 4: malignant cases. Only the positive malignant cases were followed with histological biopsy to determine the accuracy and efficiency of urine cytological examination for positive cases.

RESULTS

Majority of the cases were negative for tumour (67.19%). There were 35 cases (1.7%) that showed presence of RBCs, which could point to many lesions in the urinary tract. Twenty cases (1%) showed reactive urothelial cells only. The most common diagnostic category was acute inflammatory case (17.3%). Majority of the inflammatory cases showed acute inflammation with some reactive degenerated cells due to inflammation. Thirty-six cases showed candida hyphae with acute inflammation suggesting candida infection on cytology examination. Three cases showed trichomonas, 10 cases showed polyomavirus changes and 27 cases showed crystals with acute inflammation. Inconclusive cases constituted 11.39% of total. Majority of the cases were reported as atypical cells with significance unknown.

There were 23 (1.18%) positive cases that were diagnosed malignant on urine cytology. These 23 malignant cases were compared with histological biopsy and 22 (95.6% true-positive) cases turned out to be malignant and 1 case (false-positive) showed polyomavirus change on biopsy. Tables 1 to 4 summarize the four cytological categories with their age and gender distribution.

Table-1: Summary of benign urine cytological lesions with their gender and age distribution.

	Sex			Age Range					
Cytological Diagnosis	**Male**	**Female**	**Total**	**1-39**	**40-59**	**60-89**	**>90**	**Total**	**% of Total**
Benign									
No evidence of tumour	870	445	1315	139	492	675	9	1315	67.19
Blood in specimen	31	4	35	1	8	25	1	35	1.79
Reactive urothelial cells presents	18	2	20	—	5	15	—	20	1.02
Spermatozoa present	1	—	1	—	—	1	—	1	0.05
Subtotal Benign	920	451	1371	140	505	716	10	1371	70.06

Table-2: Summary of inflammatory urine cytological lesions with their gender and age distribution.

	Sex			Age Range					
Cytological Diagnosis	**Male**	**Female**	**Total**	**1-39**	**40-59**	**60-89**	**>90**	**Total**	**% of Total**
Acute inflammation	109	60	169	7	43	113	6	169	8.64
Acute inflammation with reactive degenerated cells with bacteria	43	28	71	1	14	46	10	71	3.63
Acute inflammation with bacteria	13	11	24	3	7	14	—	24	1.23
Acute inflammation with bacteria and candida	3	2	5	—	2	3	—	5	0.26
Acute inflammation with candida	16	15	31	4	14	13	—	31	1.58
Acute inflammation with trichomonas	1	2	3	2	1	—	—	3	0.15
Atypical cells of Polyomavirus	7	3	10		3	7	—	10	0.51
Acute inflammation with Crystals	19	8	27	2	11	13	1	27	1.38
Subtotal Inflammation	211	129	340	19	95	209	17	340	17.37

Table-3: Summary of inconclusive urine cytological lesions with their gender and age distribution.

	Sex			Age Range					
Cytological Diagnosis	**Male**	**Female**	**Total**	**1-39**	**40-59**	**60-89**	**>90**	**Total**	**% of Total**
Atypical cells favour reactive Inflammation	27	11	38	1	7	30	—	38	1.94
Atypical suspicious papillary low grade Carcinoma	7	5	12	1	4	7	—	12	0.61
Instrument reactive vs. low grade	20	3	23	3	4	16	—	23	1.18

Atypical squamous cells	3	3	6	1	3	2	—	6	0.31
Atypical significance unknown	97	12	109	4	20	83	2	109	5.57
Atypical cells suspicious for Carcinoma	29	6	35	1	6	28	—	35	1.79
Subtotal Inconclusive	183	40	223	11	44	166	2	223	11.39

Table-4: Summary of malignant urine cytological lesions with their gender and age distribution.

	Sex			**Age Range**					
Cytological Diagnosis	**Male**	**Female**	**Total**	**1-39**	**40-59**	**60-89**	**>90**	**Total**	**% of Total**
Malignant cells Present	1	—	1	—	1	—	—	1	0.05
High grade urothelial Carcinoma	20	2	22	—	2	19	1	22	1.12
Subtotal Malignant	21	2	23	0	3	19	1	23	1.18
Total	1335	622	1957	170	647	1110	30	1957	100.00

DISCUSSION

Urine cytology is primarily used for diagnosis of symptomatic patients, detection of cancer in high-risk patients (e.g., those exposed to industrial chemicals and metals, cigarette smokers, and those with schistosomiasis), and follow-up of patients with history of urinary tract neoplasia. It complements, but does not replace, cystoscopy and biopsy. However, lesions may be detected cytologically before they can be seen cystoscopically. Urinary cytologic examination is capable of detecting small or hidden lesions (e.g. in diverticuli, ureters, renal pelvis, prostatic ducts, residual urethras). Unfortunately, however, the lesions cannot be localized by cytologic study of urine.

Urinary cytology can detect most aggressive neoplasms and carcinoma in situ[4]. Patients with low-grade noninvasive tumours can be followed up cytologically[5]. Patients with negative cytologic findings have a very low risk of recurrence, while high-grade cytologic abnormalities predict an aggressive tumour course[6]. Urine cytology is also a better indicator of the presence of concomitant urothelial atypia than pre-selected mucosal biopsies[7].

Clinical history is important in proper evaluation of the specimen and should include previous diagnoses, therapy, and surgery; previous instrumentation (including catheterization); history of stones; method of specimen collection; cystoscopic findings; and any other pertinent clinical data. The most common symptoms of patients with bladder cancer are haematuria (gross or microscopic) or cystitis-like symptoms (frequency, urgency, pain).

Unfortunately, the diagnosis of urinary tract specimens is less perfect even among experts[8-14]. A review of 17 published series showed that at their worst, the false-negative rates were more than 50% for primary bladder cancer and averaged nearly 75% for papillomas[15]. An important diagnostic principle is that the higher the grade of the tumour, the more accurate the diagnosis[16-19]. In our case series, accuracy was almost 95% for high-grade malignant lesions. Urine cytology is however, not reliable in detection of renal cell or prostatic carcinoma.

As the incidence of urothelial carcinoma increases, so too does the demand for urine cytology. Accuracy of diagnosis is always important, but conservative management of bladder cancer depends on accurate cytodiagnosis. Clinical history is imperative for the reduction of misdiagnoses[16,20].

There are several reasons for diagnostic inaccuracy. Urine is an inhospitable environment for cells; consequently degenerative changes that make diagnosis difficult are common[10]. Reactive changes caused by stones, inflammation, infection, therapy among many others, as well as ‘papillary clusters’, are responsible for most false diagnoses[1,8,21-24]. In addition, transitional cells can normally show marked variation in size and shape, can be multinucleated and polyploid, and can frequently exhibit nuclear and cytoplasmic degenerative changes that can mimic malignancy. The paradox of urine cytology is that pleomorphic cells with enlarged hyperchromatic nuclei containing prominent nucleoli can be benign while cancer can be composed of nearly normal-appearing monomorphic cells with bland nuclei. The most difficult types of urinary specimens to interpret are those from the upper urinary tract (ureters and renal pelvis)[10].

False-positive diagnoses are higher in urinary cytologic specimens than in most other cytodiagnostic specimens. However, they are of less consequence because a positive cytologic diagnosis of bladder cancer should not lead directly to radical therapy[10]. A positive urine cytologic diagnosis should always be confirmed histologically before definitive therapy is instituted. False-positive diagnoses are commonly seen in cases involving stones, chemotherapy, radiation, viruses, reactive or degenerative changes, benign prostatic hyperplasia,

prostatitis, and pseudopapillary clusters. In our series we found only one false-positive case (4.4%) that showed cellular atypia on urine cytology and was proved to be polyomavirus change on biopsy.

False-negative diagnosis may be of more clinical consequence. Unfortunately, false-negative findings are also common in urine cytologic specimens. Cytologic diagnosis of papillomas and well-differentiated papillary transitional cell carcinoma (TCC) can be difficult or impossible because the cells are nearly normal appearing[10]. Also, cytologic examination of urine specimens is not very good for evaluation of primary tumours of the kidney or prostate, which exfoliate cells late or not at all.

A variety of newer diagnostic techniques, including flow cytometry[1,12,13], image analysis/ quantitative cytology[1], cytogenetics, immunology (e.g. blood group isoantigens and monoclonal antibodies to a variety of tumour-associated antigens)[1], and molecular biology have been studied in an effort to increase diagnostic accuracy. However, at least for the moment, urinary cytopathologic examination remains one of the most clinically useful means of diagnosing urothelial cancer and predicting its biologic behaviour.

REFERENCES

1. Sharma AK. Urinary cytology, simple screening procedure for lymphadenopathy. Urology 1991;38:394-6.
2. De May RM. Art and Science of cytopathology. American Society of Clinical Pathologists Press, Chicago 1999, pp 1021-39.
3. Papanikolaou A, Leontcini M. Classification of urothelial neoplasms of the urinary bladder. Hellenic Archives Pathol 2000;14(1-3):4-13.
4. Soloway MS. The Evaluation and Follow-Up of Patients With Ra, Tcis, and T1 Bladder Cancer. World J Urol 1993;11:153-5.
5. Thompson RA, Campbell EW Jr, Kramer HC. Late Invasive Recurrence Despite Long-Term Surveillance for Superficial Bladder Cancer. J Urol 1993;149:1010-1.
6. Harving N, Petersen SE, Melsen Fl. Urinary cytology in the detection of bladder tumours: Influence of concomitant urothelial atypia. Scand J Urol Nephrol Suppl 1989;125:127-31.
7. Harving N, Wolf H, Melsen F. Positive urinary cytology after tumour resection. An indicator for concomitant carcinoma *in situ*. J Urol 1988;140:495-7.
8. Farrow GM. Urine cytology in the detection of bladder cancer: A critical approach. J Occup Med 1990;32:817-21.
9. Foot NC, Papanicolaou GN, Holmqist ND. Exfoliative cytology of urinary sediments: A review of 2,829 cases. Cancer 1958;11:127-37.
10. Frable WJ, Paxson L, Barksdale JA. Current practice of urinary bladder cytology. Cancer Res 1977;37:2800-5.
11. Kern WH, Bales CE, Webster WW. Cytologic evaluation of transitional cell carcinoma of the bladder. J Urol 1968;100:616-22.
12. Koss LG, Deitch D, Ramanathan R. Diagnostic value of cytology of voided urine. Acta Cytol 1985;29:810-6.
13. Murphy WM. Current status of urinary cytology in the evaluation of bladder neoplasms. Hum Pathol 1990;21:886-96.
14. Papanicolaou GN, Marshall VF. Urine sediment smears as a diagnostic procedure in cancers of the urinary tract. Science 1945;101:519-21.
15. El-Bolkainy MN. Cytology of bladder carcinoma. J Urol 1980;124:20-2.
16. DiBonito L, Musse MM, Dudine S. Cytology of transitional-cell carcinoma of the urinary bladder: Diagnostic Yield and Histologic Basis. Diagn Cytopathol 1992;8:124-7.
17. O' Donoghue JM, Horgan PG, Corcoran M. Urinary cytology in the detection of bladder carcinoma. Irish J Med Sci 1991;160:352-3.
18. Wiener HG, Vooijs GP, van't Hof-Grootenboer B. Accuracy of urinary cytology in the diagnosis of primary and recurrent bladder cancer. Acta Cytol 1993;37:163-9.
19. Zein TA, Milad MF. Urine cytology in bladder tumours. Int Surg 1991;76:52-4.
20. Ro JY, Staerkel GA, Ayala AG. Cytologic and histologic features of superficial bladder cancer. Urol Clin North Am 1992;19:435-53.
21. Cowen PN. The development of a urological cytodiagnosis service and an evaluation of its success. J Clin Pathol 1971;24:107-12.
22. de la Rosette JJMCH, Hubregtse MR, Wiersma AM. Value of urine cytology in screening patients with prostatitis syndromes. Acta Cytol 1993;37:710-2.
23. de la Rosette JJMCH, Hubregtse MR, Meuleman EJH. Diagnosis and treatment of 409 patients with prostatitis syndromes. Urology 1993;41:301-7.
24. Psihramis KE, Hartwick W. Ureteral fibroepithelial polyp with positive urine cytology. Urology 1993;41:387-91.

Address of Correspondence:

Ibrahim Mansoor, 21441 Sloan Drive # 104B, Harper Woods, MI 48225, USA. Fax: 1-847-664-7257

Email: Ibrahim.Mansoor@stjohn.org