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Is routine urine cytology useful in the haematuria clinic?

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ABSTRACT

INTRODUCTION The objective of this study was to determine the value of routine urine cytology in the initial evaluation of patients presenting to a one-stop haematuria clinic.

PATIENTS AND METHODS A total of 1000 consecutive patients who attended the haematuria clinic between June 2003 and November 2004 were studied prospectively. A standard protocol was used to investigate these patients. This included urine cytology, upper tract imaging and flexible cystoscopy.

RESULTS Overall, 986 samples of urine were sent for cytology. In 126 patients, the report was abnormal; of these, 71 patients were found to have bladder transitional cell carcinoma by flexible cystoscopy and a further 3 had upper tract transitional cell carcinoma diagnosed radiologically. The remaining 52 patients with abnormal cytology were not found to have cancer on further investigations. The total cost for urine cytology and additional investigations was £50,535.

CONCLUSIONS In this study of the initial evaluation of patients with haematuria, no case of urothelial malignancy was diagnosed on the basis of urine cytology alone. Therefore, urine cytology need not be used routinely in the initial diagnostic work-up for haematuria.

KEYWORDS

Haematuria – Urine cytology – Urothelial malignancy – Diagnosis

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The value of urine cytology in the investigation of haematuria is debatable.[1,2] As a small minority of cases of transitional cell carcinoma may only be detected by urine cytology, it has been suggested that one can justify the cost of performing routine cytology on all new patients with haematuria.[3] The American Urological Association (AUA) best-practice policy for urine cytology recommends the test only in patients with risk factors for transitional cell carcinoma.[4]

Urine cytology may be a useful adjunct in the diagnosis of urothelial carcinoma. Overall sensitivity is, however, dependent on the degree of differentiation. Interpretation of cytology is observer-dependent and lacks a simple reproducible consensus for diagnostic criteria and terminology. Interpretation may be compromised by atypia, low cellular yield, inflammation, degenerative changes and therapeutic interventions. A fresh, uncontaminated specimen is required in order to optimise evaluation.

Performing urine cytology on all patients has significant financial and man-power implications. This study evaluates the clinical value and cost-effectiveness of urine cytology in a one-stop haematuria clinic.

Patients and Methods

A total of 1000 consecutive patients who attended the one-stop haematuria clinic, with either microscopic or macroscopic haematuria, between June 2003 and November 2004 were studied prospectively. The patients were evaluated according to a standard protocol. All patients were seen and examined by a member of the urology team and investigated on the same day. Investigations included urine cytology, blood tests as appropriate, upper tract imaging (IVU for macroscopic haematuria or ultrasound scan for microscopic haematuria) and flexible cystoscopy.

Urine samples were obtained at the time of examination before flexible cystoscopy and prepared according to a standard protocol. All abnormal results including malignant cells, suspicious cells and atypical cells were considered positive.

Table 1 Patients in the study group

	Microscopic haematuria		Macroscopic haematuria	
Total number of patients in the study	340		660	
Total malignancy diagnosed	19 (5.5%)		114 (17.2%)	
	G1-2pTa	6	G1-2pTa	41
	G1-2pT1	1	G1-2pT1	4
	G1-2pT2	0	G1-2pT2	1
	G3pTa	1	G3pTa	6
	G3pT1	5	G3pT1	23
	G3pT2>	3	G3pT2>	30
	CIS	1	CIS	3
	Renal cell carcinoma	2	Renal cell carcinoma	6
Cystoscopy positive	17		100	
Imaging positive	2 (renal cell carcinoma)		14 (8 upper tract TCC, 6 renal cell carcinoma)	
Cytology positive for transitional cell carcinoma (TCC)	9		65	

Results

In the study group, 340 patients presented with microscopic haematuria and 660 with macroscopic haematuria (Table 1). The median age was 67 years (range, 19–96 years).

A total of 986 urine samples were processed (14 samples were lost) at a combined cost of £38,454 based on our laboratory figure of £39 per sample. Following analysis, 126 patients were reported to have an abnormal result (Table 2). Of these, 71 were found to have a transitional cell carcinoma of the bladder seen at flexible cystoscopy and three had upper tract transitional cell carcinoma diagnosed on intravenous urogram, giving an overall sensitivity of 59% and specificity of 94%. (A total of 125 transitional cell carcinomas were diagnosed of which 51 had normal cytology).

Of the remaining 52 patients with abnormal cytology, 14 had GA cystoscopy with retrograde studies and ureteric washings, 17 had an additional upper tract imaging, and 24 had repeat urine cytology at a total cost of £12,081 (based on costing obtained from our hospital operating theatre and radiology department). None of these 52 patients was found to have cancer at initial assessment and, to date, none has returned with a diagnosis of transitional cell carcinoma. Of these patients with abnormal cytology, 30 were reported as showing atypical cells, 16 suspicious and 6 malignant. The total cost of urine cytology plus further investigation instigated as a result of an abnormal cytology result was £50,535.

Discussion

Cytopathological examination of cells shed in urine is undoubtedly a useful investigation in the management of urothelial carcinoma. Unfortunately, as this test lacks sensitivity for low- and intermediate-grade superficial tumours, a negative test does not rule out malignancy. This group of tumours constitutes the majority of transitional cell carcinomas. Most reported sensitivities for low-grade tumours are in the region of 30–60%.[11] Specificity is much

Table 2 Analysis of patients with an abnormal result

Tumour type	No. of cases of TCC	Cytology results (74 positive results stratified) Atypical	Suspicious	Malignant
G1-2pTa	47	3	2	2
G1-2pT1	5	1	1	1
G1-2pT2	1	1		
G3pTa	7		1	4
G3pT1	28	2		22
G3pT2 and >	33		3	29
CIS	4	1		1
Total	**125**	**7**	**7**	**60**

Table 3 American Urological Association best-practice policy for urine cytology

- Age over 40 years
- History of smoking
- Occupational exposure to chemicals or dyes
- History of gross haematuria
- History of irritative voiding symptoms
- History of recurrent urinary tract infection despite antibiotics
- History of pelvic radiotherapy, analgesic abuse and cyclophosphamide

higher but it is not possible to localise cancer based on urine cytology alone. A positive test, therefore, requires further investigation, which may be invasive and or involve radiation exposure.

The fact that new urinary markers are constantly being evaluated indicates that urine cytology is not an ideal diagnostic investigation. The reasons for this are numerous. Urine is a hostile environment for cells; consequently, degenerative changes that make diagnosis difficult are common. Reactive changes due to stones, infection, inflammation, intravesical therapy and instrumentation, as well as papillary clusters, are responsible for most false diagnoses. Giving appropriate clinical information (including instrumentation, previous treatment and the method of urine collection) enables the cytopathologist to report with greater accuracy. Non-malignant transitional cells can 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 malignant cells may appear less abnormal.

The most difficult urine specimens to interpret are from the upper urinary tract[5] because of instrumentation artefacts. A review of 17 published series showed that, at worst, the false-negative rates were more than 50% for primary bladder cancer and averaged nearly 75% for superficial low grade disease.[6] An important diagnostic principle is that the higher the grade of the tumour, the more accurate the diagnosis.[7–10] Despite the limitations, urine cytology remains very useful in the monitoring of patients with high-grade, superficial, urothelial carcinoma where sensitivity and specificity are in the region of 90%.[11]

In this study of 1000 consecutive cases of haematuria, no diagnosis of transitional-cell carcinoma (TCC) was made on the basis of urine cytology alone. The use of routine urine cytology in the initial evaluation of patients with haematuria is, therefore, difficult to justify. Fifty-two patients who had abnormal cytology reported in the initial evaluation, despite normal cystoscopy and upper tract imaging, were subjected to further evaluation with repeat cytology, further imaging or cystoscopy under general anaesthetic with retrograde studies.

There are cost and man-power implications of the test alone and also the additional investigations required to pursue an abnormal result. These investigations may cause unnecessary anxiety and morbidity.

In order to reduce the number of routine cytology requests, one can try to select those most at risk of having urothelial tumours. Using the AUA criteria (Table 3) would, unfortunately, have eliminated only 18 of our 986 requests. Having such selection criteria would, therefore, not be helpful. If we raised the age to 50 years then we could have saved a total of 18 cytology examinations. This still seems fairly unhelpful in the day-to-day running of a haematuria clinic. We believe that urine cytology should not be performed as part of the routine investigation of haematuria unless there are specific concerns such as a red bladder on cystoscopy with or without storage lower urinary tract symptoms. Although, to date, we are not aware that we have missed any urothelial carcinoma in our study group, we accept that on very rare occasions this policy might lead to the delayed diagnosis of a urothelial carcinoma. On even rarer occasions, this may be of clinical significance. We believe the balance of risk to be justified.

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