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The Role of the Bladder Tumour Antigen Test in the Management of Gross Haematuria

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ABSTRACT

Background: The bladder tumour antigen (BTA) test has been found to be more sensitive than urine cytology for the detection of recurrent bladder cancer. We chose to evaluate the role of the bladder tumour antigen test in the management of gross haematuria on initial presentation.

Methods: A prospective analysis over a 3-month period of consecutive cases of gross haematuria was conducted. Routine investigations including intravenous urogram, flexible cystoscopy, urine cytology testing and BTA testing were performed. Results were correlated with the final diagnosis, and also with histology and tumour stage in the cases of malignant outcome.

Results: The prevalence of malignancy in our series was 25.5%. Sensitivity of the BTA test was 67% and specificity 66%. This was compared to cytology which yielded a sensitivity of 66% and specificity of 100%. There were 12 cases of falsely positive results on BTA testing, giving a positive predictive value of 40%. Four cases of falsely negative results were all from superficial tumours.

Conclusion: In view of its poor sensitivity and positive predictive value, the BTA test has a limited role in the initial management of gross haematuria.

Keywords: gross haematuria, bladder tumour antigen

INTRODUCTION

Gross haematuria is one of the more common presentations to the urologist, and a very distressing symptom for the patient. In Singapore, the most common malignancy of the urinary tract is carcinoma of the bladder, in which 85% of affected patients have painless gross haematuria[1]. A separate (unpublished) study on gross haematuria done at our hospital included causes such as stone disease, infection/inflammation, benign prostatic hyperplasia, trauma, and a fair number of cases where the cause at the time of study was indeterminate. There was a prevalence rate of 22% for a malignant cause, and this risk was especially so in males over 40 years old who smoke (at least 10 years duration), presenting with painless gross haematuria with clots.

The Bard bladder tumour antigen test utilises the invasive properties of the tumour as it acts on the basement membrane or lamina propria, which provides the underlying framework for the urothelium. As a result of this interaction, protein fragments are released. These basement membrane complexes or bladder tumour antigens as they are called, combine with antigen specific antibodies linked to a colour reagent. The test involves a reagent impregnated test strip dipped into freshly voided urine. A colour change within minutes indicates the absence or presence of the bladder tumour antigen. The test is easy to perform and interpret, with rapid results.

Sarosdy et al were the first to report on the BTA test[2]. The trial was based on patients undergoing surveillance for recurrent bladder cancer after having been treated. He reported that BTA testing was more sensitive than voided urine cytology in detecting both low and high risk tumours, and gave an overall sensitivity of 41%. In a separate study based on different groups of patients ranging from healthy individuals, to sufferers of benign prostatic hyperplasia and other genitourinary diseases, he reported specificities ranging from 86% – 96%, and an overall specificity of 95.9%. D'Hallewin and Baert reported that the BTA test was superior to bladder washing cytology for diagnosing superficial bladder cancer[3]. They found a sensitivity of 65% compared to 32% with washing cytology.

Based on the above reports and the advantages alluded to about the BTA test, we decided to investigate the role of the BTA test in facilitating the early diagnosis of malignancy in cases of gross haematuria.

METHODS

We conducted a prospective analysis from October to December 1995 of consecutive cases of gross haematuria presented to the Department of Urology at the Singapore General Hospital. These patients were either admitted as inpatients to our department, or referred from other disciplines while in hospital. In addition, all outpatients seen with gross haematuria at the outpatient clinics were included in the study.

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Apart from investigations including plain X-rays, intravenous urograms and cystoscopies, voided urine was taken for BTA testing and read by our research technician within 24 hours in a blinded fashion. Urine cytologies from cystoscopic washings were sent to our pathology services. These results were correlated with the final diagnosis, and also with histology and tumour stage in cases of malignancy.

RESULTS

We accrued 56 cases of gross haematuria and excluded 9 cases of incomplete data. We eventually analysed 47 cases of gross haematuria, all of which had BTA testing performed.

The age range of the 47 patients was from 28 years to 86 years (mean 59 years), with a sex distribution of males 74%: females 26%.

The distribution of causes of gross haematuria in this study were as follows: benign prostate hyperplasia 15%, stones 15%, cystitis 19%, malignancy 25.5%, unknown cause 25.5%.

Of the 12 cases of malignancy, 9 were transitional cell carcinomas (7 bladder, 1 upper tract, 1 synchronous upper and lower tract) and 3 were renal cell carcinomas. Bleeding from benign prostatic hyperplasia and cystitis was diagnosed on flexible cystoscopy. Twelve cases (unknown 25.5%) had no working diagnoses after all the investigations, although there was one finding each of a benign bladder papilloma and a urethral polyp.

The results of our BTA testing with regards to malignant outcomes are displayed here. There was a false negative rate of 4 cases out of 12, giving a sensitivity of 67%. Twelve out of 35 cases were false positives, giving a specificity of 66%. Given our prevalence rate of malignant causes of gross haematuria as 25.5%, our positive and negative predictive values are 40% and 85% respectively (Table I).

Table I – Results of BTA testing correlating with malignant outcome

(n =) malignancy / BTA	positive	negative	total
positive	8	12	20
negative	4	23	27
total	12	35	47

Table II – Comparison of BTA testing with urine cytology

BTA test		Urine cytology	
sensitivity	67%	sensitivity	66%
specificity	66%	specificity	100%
positive predictive value	40%	positive predictive value	100%
negative predictive value	85%	negative predictive value	92%

In comparison with urine cytology, we found a marginally greater sensitivity with the BTA test of 67% against 66%, as found in previous studies. However, there was a relatively poor specificity of 66% and positive predictive value of 40% from false positive cases (Table II).

A closer look at the false positives show a fairly even distribution among various benign causes, among which there were 4 cases which tested positive for the bladder tumour antigen, but which had as yet no apparent cause. The 4 cases of false negatives were all superficial transitional cell carcinomas (Table III).

Table III – Bladder tumour antigen BTA test results

False positives	(n =)	False negatives	(n =)
BPH	2	TaG2	2
stone	2	TaG1	1
cystitis	4	T1G1	1
unknown	4		

DISCUSSION

The 25.5% prevalence rate of malignant causes of gross haematuria was obtained from a selected group of patients managed by our unit in a tertiary referral centre. At this prevalence rate, we could only be 40% confident of a true malignant cause each time the BTA tests positive. The sensitivity of BTA testing, albeit better than urine cytology (67% vs 66%), is not good enough to replace flexible cystoscopic examination where available. As a screening instrument, a negative predictive value of 85% means that 15 out of every 100 cases of malignancy causing gross haematuria would be missed in our series when the BTA tests negative.

As mentioned, there was relatively poor specificity obtained as a result of false positives from a variety of causes. With regards to the 4 cases of as yet unknown cause, whether these were false positives which could eventually turn out to be true positives is an interesting point. Indeed, in 2 other cases where a malignant cause was established, it was the BTA test which alerted us to the possibility of a malignancy, even after intravenous urography, ultrasound examination, cystoscopy and cytology had all tested negative. These 2 cases eventually turned out to be transitional cell carcinomas arising from the renal pelvis.

The false negatives for the BTA in the 4 cases of superficial tumours were not entirely surprising, recalling the mechanism of the formation of the bladder tumour antigen which involves the disruption of basement membrane proteins that comprise the complexes. We were not able to draw any correlation of BTA sensitivity with tumour grade due to our small numbers, although Sarosdy has reported increasing sensitivities with increasing tumour grades[2].

Other studies evaluating the BTA test in haematuria clinics have been presented by Khochikar, Thomas and Leyh at the European Association of Urology meeting in September

1996. Based on both microscopic and macroscopic haematuria patients[4,5], and any patient with symptoms or signs suspicious of bladder cancer[6]; the sensitivity of the BTA test was between 65% and 75%, comparable to that found in our series. Positive predictive values were similarly poor, ranging from 37% to 63%.

In conclusion, we find the bladder tumour antigen test having a limited role in the initial management of gross haematuria especially where flexible cystoscopy is readily available. However, it is possible that in selected cases, the BTA test could alert the urologist to a lurking malignancy that has proven elusive to the usual battery of investigations.

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