Half of Visible and Half of Recurrent Visible Hematuria Cases Have Underlying Pathology: Prospective Large Cohort Study With Long-Term Followup

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Purpose: Visible hematuria has a cancer yield of up to 24.2%. A large proportion of cases will have no etiology. In this study we determined the incidence of pathology (benign and malignant) in patients with visible hematuria and those with persistent and recurrent visible hematuria, and evaluated the policy for investigations.

Materials and Methods: Data were prospectively collected for 1,804 patients with visible hematuria at a United Kingdom teaching hospital from January 1999 to September 2007. In October 2010 the comprehensive hospital electronic database was checked for every individual patient to ensure no urological pathology was missed. All patients underwent standard hematuria investigations, including renal tract ultrasound and excretory urography or contrast enhanced computer tomography urogram, flexible cystoscopy and urine cytology.

Results: The male-to-female ratio was 4.8:1. Median age ± SD was 67 ± 17.0 years (range 21 to 109). Median followup was 6.6 ± 2.5 years (range 1.5 to 11.6). No urological pathology was found in 965 (53.5%) patients. Malignant urological disease was found in 386 (21.4%) patients, of whom 329 had bladder tumors. There were 32 patients with persistent visible hematuria and no malignancy. Repeat investigation was performed in 69 patients reporting recurrence. Of these patients 35 received a significant urological diagnosis, including 12 (17.4%) urological malignancies, while 34 (49.3%) still had no diagnosis. Limitations include the possibility of missing pathology.

Conclusions: Almost 50% of patients presenting with visible hematuria will have a diagnosis. Therefore, all cases of visible hematuria require full standard investigations. Patients with no diagnosis can be discharged from followup. Recurrent visible hematuria after full initial negative findings requires repeat full standard investigations because 11.6% will have malignant pathology.

Key Words: hematuria; carcinoma, transitional cell; prostatic hyperplasia

Abbreviations and Acronyms

CTU = contrast enhanced computerized tomography urogram
IVU = excretory urography
PSA = prostate specific antigen
TCC = transitional cell carcinoma
U/S = renal tract ultrasound
VH = visible hematuria

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THE incidence of urological cancer in patients presenting with VH is between 18.9% and 24.2%.[1–3] These cancers are commonly bladder and renal tumors. In addition, benign surgical disease is associated with VH in 21.4%.[3] Less than 6% of malignancy is found in cases of nonvisible hematuria.[4] VH requires urgent referral and swift evaluation.[5] Investigations usually involve U/S, IVU/CTU, cystoscopy and urine cytology.[2] Despite full investigations a significant proportion of patients will receive no etiological diagnosis,[1] and there is uncertainty as to the cause in these patients who are evaluated with no pathology found. The persistence or recurrence of VH

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may provoke further investigations, but followup for patients with recurrent VH is unclear.

At what stage can patients with no recurrence be safely discharged? What is the likelihood of recurrence and the possibility of a subsequent urological cancer diagnosis? The paucity of information in the literature regarding the natural history of VH after initial negative investigations explains the dearth of guidelines for clinical practice. This has resulted in the lack of a consistent approach. A recent long-term prospective analysis confirmed that patients with nonvisible hematuria and negative investigations were extremely unlikely to have significant urological disease, and that they need repeat investigations only if VH develops subsequently.[6] Does the same apply to patients with visible hematuria? In this study we determined the incidence of pathology (benign and malignant) in patients with new VH and in those with persistent or recurrent VH, and established a policy for investigations.

PATIENTS AND METHODS

Study Period

This study included all new patients attending a hematuria clinic at a large university teaching hospital between January 1999 and September 2007. Before referral by primary care physicians all patients with VH underwent routine blood tests which included full blood count, renal function, coagulation profile and urinalysis to rule out infection. In October 2010 the comprehensive hospital electronic database (which includes pathology and radiology) was checked for every individual patient to ensure no urological pathology was missed.

Protocol

The protocol for investigation of VH was U/S and IVU/CTU to image the upper tracts, flexible cystoscopy and urine cytology. For persistent VH after standard investigations, watchful waiting, medical treatment with 5α-reductase inhibitors and nephrological referral were performed, considering each case on its own merits. CTU replaced IVU for high risk patients (patients older than 50 years, smokers, and those with a family history of bladder cancer and previous pelvic radiotherapy). The policy was to investigate all patients with VH as per the standard hematuria protocol regardless of anticoagulation status (provided it is within therapeutic levels), duration or intensity of hematuria. Patients with recurrent VH (more than 1 year after full standard initial investigation) were reinvestigated with the same protocol as the initial investigation.

Followup

After the initial negative investigation, if hematuria settled, patients were discharged. Patients and primary care physicians were informed that after discharge if hematuria recurred, they needed to be re-referred. One year was arbitrarily considered safe before full standard investigations were repeated.

Database

Data were prospectively collected on a Microsoft Access database for research and analysis. Data set included age, gender and smoking history. All data were independently maintained, and the results and information were independently checked by 2 authors (RV and BKS).

Diagnostic Quality

All first episode and recurrent hematuria referrals were vetted by a consultant urologist. All flexible cystoscopy were performed by a consultant urologist, a senior or supervised junior trainee or an experienced oncology nurse practitioner. The U/S and IVU were done as a part of the hematuria clinic and reported in a standardized fashion by trained radiographers or radiologists. The CTU was reported by an experienced radiologist. When doubt existed, the case was discussed in a multidisciplinary meeting.

Data Analysis

The point of last followup (October 2010) was at least 3 years from the end of the study period (1999 to 2007). In October 2010 the records of each individual patient in the comprehensive hospital electronic radiology and pathology database were checked to ensure that no pathology was missed. Final analysis for the full cohort of patients was then completed.

RESULTS

A total of 1,804 patients with VH were investigated during the study period. The male-to-female ratio was 4.8:1. Median patient age was 67 $\pm$ 17.0 years (range 21 to 109). Median followup was 6.6 $\pm$ 2.5 years (range 1.5 to 11.6). No pathology was found in 965 (53.5%) patients. Malignant urological disease was found in 386 (21.4%) patients, of whom 329 had bladder tumors, 39 renal tumors, 10 prostate cancers and 8 upper urinary tract tumors. The remaining patients had benign pathology (table 1).

When patients were grouped according to smoking history, smokers had a higher incidence of bladder cancer and these patients also had a higher stage and grade of cancer ($p < 0.05$, table 2). Ex-smokers were defined as those who had stopped smoking at the time of their investigations. Of the

Table 1. *Urological pathology in patients with VH*

	No. Pts (%)
No pathology	965 (53.5)
Bladder tumor	329 (18)
Renal tumor	39 (2.2)
Upper tract TCC	8 (0.4)
Prostate Ca (+ high PSA)	10 (0.6)
Metastatic disease	3 (0.2)
Large bleeding prostate	242 (13.4)
Cystitis/urinary tract infection	36 (2.0)
Renal/ureteral calculi/hydronephrosis	99 (5.5)
Bladder stone	36 (2.0)
Urethral stricture	37 (2.1)