

THE ROLE OF CYSTOSCOPY IN THE EVALUATION OF HEMATURIA IN THE PRESENCE OF NORMAL RADIOLOGICAL AND MICROBIOLOGICAL WORK-UP

**Cenk Yazıcı, M.D. / Tufan Tarcan, M.D., PhD, / Levent Türkeri, M.D., Ph.D.
Yalçın İlker, M.D. / Ferruh Şimşek, M.D.**

Department of Urology, School of Medicine, Marmara University, Istanbul, Turkey.

ABSTRACT

Objective: The etiology of microscopic and macroscopic hematuria may range from conditions posing minimal risk to the patient to potentially life-threatening conditions. There are controversial ideas about the evaluation of hematuria. In this survey, we examined the necessity of cystoscopy in patients with microscopic and macroscopic hematuria who were radiologically and microbiologically normal.

Methods: A total of 139 patients with microscopic or macroscopic hematuria who were microbiologically and radiologically normal and had cystoscopy between 1991 and 2003 were retrospectively analyzed. Routine history, physical examination, routine blood tests, urine analysis, urine culture, a plain radiography, urinary system ultrasonography / intravenous pyelography, computerized tomography and tuberculosis tests, including ARB-Bactec were unable to diagnose a pathology to identify the reason for hematuria, and cystoscopy was performed on all patients.

Results: Seventy five (53.9%) patients were male and 64 (46.1%) were female. There was no pathology in 86 (61.8%) patients in diagnostic cystoscopy whereas, 21(15.2%) had a papillary tumor and 16 (11.5%) had a suspicious lesion in the bladder that was

biopsied. In 16 (11.5%) patients prostatic hypertrophy was the only cystoscopic finding. According to the histopathological examination, 15 (93.5%) of the suspicious lesion biopsies were benign, but 1 (6.5%) patient had carcinoma in-situ. All of the papillary lesions were reported as superficial transitional cell carcinoma (TCCA). Overall, TCCA was detected in 4(4.9%) and 18(31%) patients with microscopic and macroscopic hematuria, respectively. Irrespective of the type of the hematuria, none of the patients under 40 years of age were found to have bladder cancer.

Conclusion: Our findings indicate that all patients older than 40 years of age with microscopic and macroscopic hematuria should undergo a cystoscopy. The current study further suggests that patients younger than 40 years of age with microscopic hematuria can only be safely followed up with non-invasive methods, without performing cystoscopy.

Key Words: Microscopic, Macroscopic, Hematuria, Cystoscopy, Diagnosis

INTRODUCTION

Hematuria is the presenting symptom in 85-90% of patients with bladder cancer; it may be gross

or microscopic and intermittent or constant. It is mandatory to fully investigate such patients to exclude an underlying genitourinary malignancy (1,2). The etiology of microscopic and macroscopic hematuria may range from conditions posing minimal risk to the patient, such as renal cyst, to potentially life-threatening conditions, predominantly including malignant tumors that must be distinguished from many other more common benign diseases (3). Macroscopic hematuria is common with a community prevalence of 2.5% (4) and estimated to account for 4% to 20% of all urological visits (5). Microscopic hematuria is a common clinical problem that has a 1% to 13% prevalence in adults (6).

There are controversial ideas about the evaluation of hematuria that some authors reported such as: "hematuria of any degree should never be ignored, and in adults, it should be regarded as a symptom of urological malignancy until proven otherwise (7)" and "microscopic hematuria detected during a screening examination should probably not be regarded as a specific sign of a significant lesion and does not itself warrant urological investigation in adults aged 40 or less" (8). In the literature, the incidence of urogenital carcinoma in patients with microscopic hematuria is reported to range between 2.2% and 14.3% (9,10).

The established urological evaluation of hematuria has undergone little change during the years and consists of urine analysis, urine culture, an upper urinary tract radiological study (intravenous pyelography (IVP) or urinary tract ultrasonography (USG)), tuberculosis tests, cytology and cystoscopy. As urological investigations fail to find the cause of isolated microscopic hematuria, an actual clinical problem for urologists is how extensively to evaluate young patients with microscopic hematuria in whom the incidence of malignancy is low. Cystoscopy which is one of the essential examinations in evaluation of hematuria can cause great discomfort to the patients and is an economic problem for both patients and government.

In this survey, we examined the necessity of cystoscopy in patients with microscopic and

macroscopic hematuria who were radiologically and microbiologically normal.

MATERIAL AND METHODS

A total of 139 patients with microscopic or macroscopic hematuria who were microbiologically and radiologically normal and had cystoscopy between 1991 and 2003 were retrospectively analyzed. Microscopic hematuria is defined as, over 3 erythrocyte per high-power field in an urine sample. A routine history, physical examination, routine blood tests, urine analysis, urine culture, a plain radiography, urinary system ultrasonography / intravenous pyelography, computerized tomography and tuberculosis tests, including ARB-Bactec, were performed to all patients before cystoscopy. Computerized tomography without contrast medium was used in patients if a stone was suspected. These analyses were unable to indicate a pathology to identify the reason of hematuria. Persistent microscopic hematuria was defined as detected in minimum 3 urinalyses. All of the patients' microscopic hematuria were persistent. Cystoscopy was performed under general anesthesia where the whole uretra, prostate, and bladder were screened for suspicious lesions and urine expulsion from ureteral orifices was observed. Any lesion found during cystoscopy was biopsied or resected. The specimens were analysed by the Department of Pathology at Marmara University. All of the patients had a minimum 1 year follow-up. The statistical analysis of the results was done by Q-square test.

RESULTS

The mean age of patients was 54.4 years (26-72). Seventy-five (53.9%) patients were male with a mean age of 54.5 years (26-72) and 64 (46.1%) patients were female with a mean age 54.3 years (31-64).

Eighty-one (58.2%) patients were evaluated due to microscopic hematuria and 37 (45.7%) of these patients were male with a mean age of 54.5, on the other hand, the number of patients evaluated for macroscopic hematuria was 58(41.8%). Thirty-eight (65.5%) patients of this group were male with a mean age of 54.5. The

number of female patients for each group was 44 (54.3%) and 20 (34.5%) with a mean age of 54.3 for both groups, respectively ($p=0.03$).

When the patients were grouped according to age, 109 (78.4%) patients were >40 years and 30 patients were <40 years of age. Microscopic hematuria was seen in 76.7% of patients <40 years and 39.4% of patients >40 years of age, on the other hand, macroscopic hematuria was a symptom in 23.3% of patients <40 years and 60.6% of patients >40 years ($p=0.003$). The demographic properties of the patients are summarized in table I.

Table I: Relation between the type of hematuria, gender and age.

	Gender		Age	
	Female No of pts (n) (Percent (%))	Male No of pts (n) (Percent (%))	<40 years No of pts (n) (Percent (%))	>40 years No of pts (n) (Percent (%))
Microscopic hematuria	44 (54.3%)	37 (45.7%)	23 (76.7%)	43 (39.4%)
Macroscopic hematuria	20 (34.5%)	38 (65.5%)	7 (23.3%)	66 (60.6%)
Total No of pts (n) (Percent (%))	64 (100%)	75 (100%)	30 (100%)	109 (100%)
	*$p=0.03$		**$p=0.003$	

* Statistically significant difference between male and female patients in terms of the type of hematuria.

** Statistically significant difference between the age groups in terms of the type of hematuria.

Cystoscopic findings of the patients are listed in table II. Cystoscopy detected no pathology in 86 (61.8%) patients, whereas 21(15.2%) had a papillary lesion, 16(11.5%) had suspicious lesion that had been biopsied and 16(11.5%) patients had obstructive changes in the bladder due to BPH. As we subdivide the group according to the type of hematuria, 75.3% of patients with microscopic hematuria had entirely normal cystoscopy findings. This ratio was 43.1% for patients with gross hematuria ($p=0,001$). A papillary lesion was detected in 4.9% of patients with microscopic hematuria and 29.3% of patients with macroscopic hematuria ($p=0.001$).

The cystoscopic findings according to age group are listed in table II. There was no pathology on cystoscopy in 76.7% of patients younger than 40 years and 57.8% of patients who were >40 years ($p=0,04$). None of the patients <40 years had papillary lesions on cystoscopy and 23.3% patients had suspicious lesions. In the patients over 40 years, 19.2% had a papillary lesion, 8.3% had a suspicious lesion and 14.7% had obstructive changes in the bladder due to BPH ($p=0,02$).

As a result, resection and biopsy performed to a total of 37 patients and 22 (15.8%) patients

Table II: The relation between the cystoscopic findings, type of hematuria and age of patients.

	No pathology No of pts (n) (Percent (%))	Papillary lesion No of pts (n) (Percent (%))	Suspicious lesion No of pts (n) (Percent (%))	Obstructive changes No of pts (n) (Percent (%))	Total No of pts (n) (Percent (%))
Microscopic hematuria	61 (75.3%)	4 (4.9%)	6 (7.5%)	7 (8.6%)	81 *(100.0)
Macroscopic hematuria	25 (43.1%)	17 (29.3%)	10 (17.2%)	9 (15.6%)	58 *(100.0)
	*$p=0.001$	**$p=0.001$	***$p=0.12$	****$p=0.36$	
<40 years of age	23 (76.7%)	0 (0.0%)	7 (23.3%)	0 (0.0%)	30 (100.0%)
>40 years of age	63 (57.8%)	21 (19.2%)	9 (8.3%)	16 (14.7%)	109 (100.0%)
	+$p=0,04$	++$p=0,02$	+++$p=0,06$	++++$p=0,02$	
Total (n)	86	21	16	16	139

* Statistically significant difference between normal cystoscopic findings in terms of the type of hematuria.

** Statistically significant difference between papillary lesions in cystoscopy in terms of the type of hematuria.

*** No statistically significant difference between suspicious lesions in cystoscopy in terms of the type of hematuria.

**** No statistically significant difference between obstructive changes in the bladder in terms of the type of hematuria.

+ Statistically significant difference between normal cystoscopic findings in terms of age groups.

++ Statistically significant difference between papillary lesions in cystoscopy in terms of age groups

+++ Statistically significant difference between suspicious lesions in cystoscopy in terms of age groups.

++++ Statistically significant difference between obstructive changes in the bladder in terms of age groups

indicated pathologically proven bladder tumor. The histopathological results are listed in table III. All of the papillary lesions were reported as transitional cell carcinoma. On the other hand, only 1 of 16 (6.2%) suspicious lesions was reported as carcinoma in-situ. All other biopsies were reported as benign lesions related to cystitis. Bladder tumor was diagnosed in 4 (4.9%) patients with microscopic and 18 (31.0%) patients with macroscopic hematuria ($p=0.001$).

When we analyzed the results according to age group, we observed that there was no bladder tumor in patients under 40 years of age. Indeed, all of the bladder tumors were observed in patients over 40 years of age ($p=0.001$). The age group of patients with bladder tumor was 45-72 (mean:65).

The pathology of all bladder tumors was superficial. There was only one patient with carcinoma in-situ, who had admitted to our clinic with macroscopic hematuria. He was 62 years of age. As we subdivide the tumor pathologies, 12 (57.1%) patients' pathology was Ta and 9 (42.9%) patients' pathology was T1 ($p=0.25$).

DISCUSSION

The value of cystoscopy in the evaluation of macroscopic hematuria is undebatable. The prevalence of bladder cancer with macroscopic hematuria was reported to be 22-35% (11,12). Indeed, most of these studies were designed to evaluate the prevalence of bladder tumor in the whole group of patients with macroscopic hematuria (whether radiologically or microbiologically normal or not). In the present study, we evaluated only patients with macroscopic hematuria who were radiologically and microbiologically normal and found a bladder tumor in 31% of patients. This result points out the necessity for cystoscopy in patients with macroscopic hematuria.

The crucial point of discussion is where and when we need cystoscopy in the evaluation of microscopic hematuria. Microscopic hematuria (symptomatic or asymptomatic) can be seen widely in urology clinics. Froom et al (8) found that 38.7% of young men between 18-33 years of age had microscopic hematuria at some point over a 15 year follow-up period. However, the prevalence of bladder cancer in patients with microscopic hematuria is much lower than in

Table III: Relation between the pathologic diagnosis of patients and type of hematuria, age of patients and smoking.

	Transitional cell carcinoma No of pts (n) (Percent (%))	Carcinoma in-situ No of pts (n) (Percent (%))	Nonspecific cystitis No of pts (n) (Percent (%))	Eosinophilic cystitis No of pts (n) (Percent (%))	Total No of pts (n) (Percent (%))
Microscopic hematuria	4 (40%)	0 (10%)	5 (50%)	1 (10%)	10 (100%)
Macroscopic Hematuria	17 (63.0%)	1 (3.7%)	8 (29.6%)	1 (3.7%)	27 (100%)
*p=0.001					
<40 years of age	0 (0.0%)	0 (0.0%)	7 (87.5%)	1 (12.5%)	8 (100%)
>40 years of age	21 (72.5%)	1 (3.4%)	6 (20.7%)	1 (3.4%)	29 (100%)
**p=0.001					
Non-smoker	6 (42.9%)	1 (7.1%)	5 (35.7%)	2 (14.3%)	14 (100%)
Smoker	15 (65.2%)	0 (0.0%)	8 (34.8%)	0 (0.0%)	23 (100%)
***p=0.28					
Total	21	1	13	2	37

* Statistically significant difference between microscopic and macroscopic hematuria in terms of the incidence of bladder cancer.

** Statistically significant difference between the age groups in terms of the incidence of bladder cancer.

*** No statistically significant difference between cigarette smoking in terms of the incidence of bladder cancer.

macroscopic hematuria which was reported as 2.5% to 20% in population-based studies (13-16). Khadra et al, found that the risk of bladder tumor in patients with macroscopic hematuria was 4 times greater than in microscopic hematuria and they reported the bladder cancer prevalence as 9.4% of 982 patients with microscopic hematuria (12). In another study, Suzuki et al reported 3% of patients with microscopic hematuria had bladder cancer (3). Britton et al (13) found 5.3% and Mayfield et al (16) found 5% prevalence for this group of patients. In our study, we found bladder cancer in 4.9 % of patients with microscopic hematuria who were radiologically and microbiologically normal ($p=0,001$). Therefore, other factors in patients with microscopic hematuria must be questioned before deciding on the need for cystoscopy.

Age seems to be an important factor for deciding on the need for cystoscopy in patients with hematuria. Thompson reported no malignancy in patients with microscopic hematuria who were under 40 years of age (17). In another study, Murakami et al, reported that all of the patients with bladder cancer found in cases with microscopic hematuria were older than 40 years (18). Kupor and Topham proposed that patients aged <50 years and with microscopic hematuria could be managed with little or no urological investigation and should probably be referred for a nephrological opinion (19,20). The same results were also noted by Khadra et al.(12). In the present study we also did not detect any malignancy in patients <40 years of age. On the other hand, the youngest patient who had bladder cancer was 45 years old and the mean age of cancer patients was 65 years. There was a statistically significant difference between bladder cancer seen < 40 years and > 40 years of age ($p=0,001$). Therefore, cystoscopy is necessary in patients older than 40 years, whether the hematuria is microscopic or macroscopic. On the other hand, for patients with microscopic hematuria, cystoscopy is more valuable for patients >40 years of age than patients < 40 years of age.

Cigarette smoking is a well known risk factor for bladder tumors. Grossfeld et al proposed that

cystoscopy for the evaluation of microscopic hematuria is recommended for all adults over 40 years and for those under 40 years with risk factors for the development of bladder cancer such as a smoking history, occupational chemical exposure or history of irritative voiding symptoms (21). We also evaluated the relation between bladder tumors and cigarette smoking. Sixty eight percent of the patients who had bladder cancer were smokers. On the other hand, 58.6% of patients who had no bladder cancer were smokers. We could not find a significant relation between cigarette smoking and bladder cancer ($p=0.28$), but the number of patients was not high enough to allow an exact decision on the subject.

Other questions to be answered are: 1- What happens to patients with microscopic hematuria who are cystoscopically normal during the follow-up period? 2- Do we need to repeat cystoscopy after a period of follow-up? Studies showed that urologic malignancy was subsequently diagnosed in the follow-up of 1-3% of those with microscopic hematuria (18-22). Howard and Grolin, in a 10 to 20 year follow-up of 155 patients with persistent hematuria showed that urothelial cancer did not develop in patients with a previous negative work-up (23). In our study group, we followed-up the patients for a median of 4 years (1-8 years). No pathological diagnosis was detected during the follow-up period. We propose to follow up the patients with unexplained microscopic hematuria with non-invasive methods.

Cystoscopy is still the most valuable diagnostic tool in patients with hematuria. However, it is an invasive and costly procedure which may be associated with morbidity related to anesthesia (if used), infection and endoscopic trauma. Our findings indicate that all patients older than 40 years of age with unexplained microscopic or macroscopic hematuria should undergo a cystoscopy. The current study further suggests that patients younger than 40 years of age with an unexplained microscopic hematuria can only be safely followed up with non-invasive methods, without performing cystoscopy whereas macroscopic hematuria in this age group also warrants cystoscopic evaluation.

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