Evaluation of the Patient with Asymptomatic Microscopic Hematuria

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Asymptomatic microscopic hematuria (AMH) is relatively common in clinical practice but the etiology remains unclear in the majority of patients; it is rarely related to genitourinary malignancies. The 2012 guidelines of the American Urological Association recommend an evaluation after a single positive urinalysis with mandatory upper tract evaluation in all patients, preferably with CT urography (CTU). The likelihood of detecting significant upper track abnormalities, particularly malignancies is low with CTU, while incidental extraurinary abnormalities are often found, the majority of which are not clinically significant. The workup for these incidental findings has significant financial and clinical implications. Primary care physicians, who are most apt to encounter patients with AMH, have a low rate of adherence to the AUA guidelines, possibly as a result of the broadening of criteria for AMH evaluation by the AUA, with resultant uncertainty amongst primary care physicians about the appropriate candidates for such evaluation. Selection of subgroups of patients with risk factors for GU malignancies who may benefit from a complete evaluation is essential, as opposed to evaluation of all patients classified as having AMH.

Key Words: Microscopic hematuria; AUA guidelines; CTU; extraurinary findings.

Hematuria has long been the subject of controversial medical inquiry. In an 1887 article on the diagnostic significance of hematuria, Robert Saundby stated that "hematuria is a symptom common to a number of pathologic conditions, which differ essentially in their seat, nature, and relationships" (1). Henry Wade, in a lecture to the British Medical Association in 1932, opined that the cause of hematuria "may be simple and its cure easy; but, on the other hand, it may end in the patient's death" (2). Thus, even in an early era of medicine, it was recognized that hematuria was often only a symptom of a wide spectrum of urologic diseases. In the intervening years since these early publications, the ability to rapidly and easily detect hematuria, specifically microscopic hematuria, has evolved and become readily available. Therefore, we are now faced with increasing numbers of patients who undergo evaluation for asymptomatic microscopic hematuria (AMH) in efforts to detect an occult genitourinary malignancy, primarily bladder cancer, and upper tract urothelial cancer (3–9). In this review, we examine the literature regarding the evaluation of patients with AMH. The evaluation and management of patients with gross visible hematuria will not be addressed in this review.

DEFINITION AND EVIDENCE-BASED GUIDELINES

Microscopic hematuria is defined as the presence of more than three red blood cells (RBC) per high-power field (HPF) in a properly collected specimen of urine in the absence of contamination, infection, or other benign causes (6). AMH is relatively common (7), and its prevalence is estimated to be approximately 2.5%–13% of adult men and postmenopausal women in population-based screening studies (7,8). The etiology of AMH remains unknown in most cases (61%–77%), whereas a genitourinary malignancy is detected in only 0.43%–3.4% of patients (9–11).

The American Urological Association (AUA) developed a best practice statement in 2001 and formal evidence-based guidelines in 2012 (6,12,13) to provide a clinical framework for the diagnosis, evaluation, and follow-up of AMH. The most recent AUA guidelines recommend an evaluation after a single positive urinalysis (hematuria on microscopy, not dipstick alone) (6). The evaluation includes a history, physical examination, and laboratory studies to exclude obvious benign causes (6). Voided urine cytology is no longer necessary, except in patients with risk factors for malignancy (6). Additional evaluation with a cystoscopy is required for all patients aged >35 years or any patient with risk factors for malignancy such as irritative voiding symptoms, current or past tobacco use, and chemical exposures, regardless of age (6).

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Finally, imaging is deemed mandatory for all patients, preferably with multiphasic computed tomography urography (CTU) for the evaluation of the upper urinary tract (6,14).

GENITOURINARY TRACT FINDINGS AT EVALUATION

The etiology of AMH is rarely related to a genitourinary malignancy. In a study of 1034 patients who were evaluated with a standard regimen of urine culture, urine cytology, blood chemistry, intravenous pyelography, and cystoscopy, an etiology was identified in only 45% of cases (15). In these cases, a highly significant lesion, such as malignancy, requiring immediate treatment was identified in only 2.9% of patients (15). In the remaining cases with an etiology, 18.9% had moderately significant lesions, such as urolithiasis or glomerular disease requiring delayed treatment (15). Finally, 23.8% of cases had insignificant lesions, which were deemed not likely to be the cause of the hematuria (15). Similar rates for detection of both benign and malignant disease have been reported by other studies (7,10,16).

In an investigation of over 150,000 patients with more than three RBC/HPF in the urine sediment on microscopy, the rate of genitourinary malignancy was only 0.68% (9). The only groups which exceeded the rate for the overall cohort were men aged >40 years with three or more RBC/HPF (range, 1.2%–6.11%, depending on degree of hematuria) and women aged >40 years with ≥25 RBC/HPF (range, 0.87%–1.77%, depending on degree of hematuria) (9). Although the authors concluded these are high-risk groups, the rates of malignancy detection were still relatively low (9).

A recent prospective study attempted to identify patients with AMH who were most at risk for a renal or bladder malignancy (11). Not surprisingly, the overall rate of malignancy was very low with 2.3% and 0.2% of patients being diagnosed with a pathologically confirmed bladder and renal cancer (none were diagnosed with an upper tract urothelial carcinoma), respectively (11). When examining the benign but significant findings, nephrolithiasis, prostatic bleeding, urinary tract infections, and glomerular disease were detected in 16.2%, 4.0%, 2.3%, and 0.9% of patients, respectively. Male gender, age >50 years, and a previous history of gross hematuria were all significantly associated with detection of malignancy (11). A hematuria risk index was developed by these investigators to classify patients into a low-, moderate-, and high-risk group on the basis of the model developed in their investigation (11). The risk index was predictive of cancer detection with the high-risk group demonstrating an 11.6% cancer detection rate and low-risk group 0.2% cancer detection rate, respectively (11). The authors concluded that patients <50 years without a history of gross hematuria could safely avoid evaluation with cystoscopy and CTU (11). Male sex was predictive of cancer detection, but interestingly, smoking history and ≥25 red blood cells per high-power field on a recent urinalysis were not found to be statistically significant risk factors. These authors also stated that AMH was a poor predictor of renal cell cancer.

As the previous discussion makes clear, the detection rate of a genitourinary malignancy in a patient with AMH is very low. Clinically significant benign lesions are also detected when patients with AMH undergo a workup, but in most patients, no etiology is identified to explain the microscopic hematuria.

IMAGING STUDIES IN EVALUATION OF AMH

Excretory urography (EU), a study also known by the synonyms "intravenous urography"and "intravenous pyelogram", was previously the gold standard for the radiographic evaluation of the genitourinary tract for parenchymal and urothelial abnormalities. However, the chief drawback of an excretory urogram was the poor sensitivity for detection of small renal masses (17). With improvement in CT technology, multiphasic CTU gained ascendancy in the evaluation of the urinary tract and is now the preferred imaging modality for the evaluation of patients with both gross and microscopic hematuria (6). In patients with microscopic hematuria, CTU has a reported sensitivity of 64%, a specificity of 98%, a positive predictive value of 76%, and a negative predictive value of 96% in the detection of a genitourinary tract cancer (17).

A study that compared CTU with noncontrast CT in the evaluation of AMH (18) in 442 patients showed no malignancy-related hematuria findings, 64 non–malignancy-related hematuria findings (of those 62 were renal calculi), and 138 incidental non–hematuria-related findings. The authors concluded that CTU added no additional diagnostic benefit versus unenhanced CT in evaluating the upper urinary tracts of adults aged <50 years with AMH, with a <1.0% risk of missing upper urinary tract hematuria-related malignancy. A Danish study (19) that retrospectively assessed the results of CTU in 771 patients with hematuria over a 1-year period found no malignancies in the kidneys or ureters in 376 patients with microscopic hematuria. These studies reassert the low likelihood of the presence of upper tract abnormalities, particularly malignancies, in patients with AMH.

EXTRAURINARY FINDINGS AT IMAGING EVALUATION FOR AMH

With the increasing utilization of CTU, it is now common to find incidental extraurinary abnormalities during the evaluation of a patient with hematuria (3–5). In an investigation of 344 consecutive patients who underwent a CTU for hematuria, 75.3% of patients were found to have 568 extraurinary abnormalities (4). However, only 12.5% of the findings were characterized as highly significant with the majority being either an indeterminate lung nodule or lymphadenopathy (4). The remaining 39.1% and 48.4% were determined to be of moderate and low clinical significance, respectively (4). In a more recent investigation of