Evaluation of Microscopic Hematuria: A Critical Review and Proposed Algorithm

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Microscopic hematuria (MH), often discovered incidentally, has many causes, including benign processes, kidney disease, and genitourinary malignancy. The clinician, therefore, must decide how intensively to investigate the source of MH and select which tests to order and referrals to make, aiming not to overlook serious conditions while simultaneously avoiding unnecessary tests. Existing professional guidelines for the evaluation of MH are largely based on expert opinion and have weak evidence bases. Existing data demonstrate associations between isolated MH and various diseases in certain populations, and these associations serve as the basis for our proposed approach to the evaluation of MH. Various areas of ongoing uncertainty regarding the appropriate evaluation should be the basis for ongoing research.

Key Words: Microscopic hematuria, Diagnosis, Evaluation, ESRD, Genitourinary cancer

Microscopic hematuria (MH), often discovered incidentally by clinicians, can arise from anywhere along the urinary tract and has an extensive differential. At one end of the spectrum, it may be because of a benign process, such as menstrual contamination or vigorous exercise. Alternatively, it may be the presenting sign of a genitourinary (GU) malignancy. Given this wide range of potential causes, the medical practitioner who identifies MH is faced with the decision of whether this finding requires further investigation and, if so, how intensively to proceed. Available tests for the workup include urine microscopy and serum-based tests of kidney function, imaging studies, and cystoscopy. In addition to identifying the cause, the goal in evaluating MH is to make certain that serious medical conditions are not overlooked while simultaneously avoiding unnecessary tests, especially those tests with serious potential risks. Several professional medical associations have offered recommendations for the evaluation of MH.[1-3] The evidence supporting existing guidelines, however, is limited and largely based on expert opinion. In this review, we focus on asymptomatic, persistent MH in adults that is not accompanied by overt proteinuria, reduced kidney function, or gross hematuria. We summarize existing data on the association between MH and various diseases and critically examine current guidelines for its evaluation. We conclude with a proposed approach to the evaluation of MH.

EPIDEMIOLOGY

MH is found in a substantial proportion of adults, although precise prevalence estimates vary depending on age, sex, and other patient characteristics. Variable definitions of MH also affect these estimates, with some studies using dipstick-based definitions and others relying on urine microscopy to determine presence of MH. Among 17 MH-screening studies referenced by the 2012 American Urology Association (AUA) guideline for the evaluation of MH, prevalence ranged from less than 3% to more than 20%, with higher rates found among older men, men with smoking histories, and individuals with repeated urine testing.[1] A screening study of young, healthy adults serving in the Israeli military found that among 1000 asymptomatic male Air Force personnel, aged 18 to 33 years, 16.1% had at least 2 to 4 red blood cells per high-powered microscopic field (RBC/hpf) on multiple annual examinations within a 5-year period.[4] Another more recent study of more than 1.2 million young adults and adolescents of both sexes who underwent screening urinalyses before joining the Israeli military demonstrated a 0.3% prevalence of persistent, asymptomatic MH, defined as at least 5 RBC/hpf on 3 separate occasions.[5]

DIFFERENTIAL DIAGNOSIS

MH can arise from any portion of the GU tract, from the glomerulus to the urethra[6-12] (Table 1). Urine microscopy can generally differentiate glomerular from nonglomerular hematuria, a distinction that has implications for focusing the workup. Dysmorphic RBCs (particularly acanthocytes) or RBC casts found in the urine sediment are specific findings that suggest a glomerular cause of MH, such as immunoglobulin A (IgA) nephropathy, thin basement membrane nephropathy, or hereditary nephritis. Nonglomerular causes of MH are further categorized based on the location of bleeding within the urinary tract. Upper tract lesions involving the kidney and/or ureters include parenchymal disease, such as cystic diseases, pyelonephritis, kidney infarction, medullary sponge kidney, or papillary necrosis. Additional upper tract causes of MH also include nephrolithiasis/urolithiasis, sickle cell disease, or neoplastic diseases, such as kidney cell or urothelial carcinoma. In addition to benign and malignant bladder neoplasms, lower tract causes of MH include prostatitis, urethritis, cystitis, benign prostatic hyperplasia, or urethral stricture.

The likelihood of a particular cause of MH partially depends on a patient's demographic and clinical characteristics. For example, a young, otherwise healthy woman with

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previous nephrolithiasis has a higher probability of recurrent kidney stones as the cause of MH, whereas an older man with a longstanding smoking history is more likely to raise concern for possible bladder cancer as the cause. Careful consideration of the patient's history and physical examination is crucial for determining a diagnostic approach.

ASSOCIATIONS WITH DISEASE

With the exception of hereditary nephritis,[13] the finding of isolated glomerular MH has traditionally been associated with a benign course. However, kidney biopsy data from patients with isolated MH suggest that this may not be the case.[14-17] Although conditions such as IgA nephropathy and thin basement membrane nephropathy often present with MH alone, they may be associated with later development of proteinuria or reduced kidney function.[18,19] The presence of MH has been associated with the subsequent development of even more serious kidney disease, including ESRD. A recent study from Israel reported an increased risk of ESRD among young adults and adolescents with persistent isolated MH after controlling for age, sex, paternal country of origin, body mass index, baseline blood pressure, and period of enrollment.[5] The authors concluded that persistent MH may, therefore, represent an early sign of occult kidney pathology that necessitates further investigation and follow-up as it may evolve into more clinically apparent kidney disease.

CLINICAL SUMMARY

- Microscopic hematuria (MH) is associated with a large array of causes, ranging from benign conditions to more serious ones, the latter including end-stage kidney disease and genitourinary malignancy.
- Following urinary microscopic confirmation of MH, evaluation involves several potential strategies, including nephrology workup, imaging and cystoscopy.
- Evidence supporting specific approaches to evaluate MH is weak, particularly regarding an age threshold to perform cystoscopy.
- Clinical judgement is therefore necessary in selecting the appropriate evaluation strategy for an individual patient.

In Japan, where IgA nephropathy is prevalent, Iseki and colleagues[20] followed over 100,000 individuals who underwent a community-based urine dipstick screening program and subsequently monitored them for incident ESRD over 17 years of follow-up. Among male subjects, hematuria detected by dipstick was an independent predictor of ESRD.[20] Other studies have demonstrated a significant association between MH and later development of proteinuria. For example, Ramirez and coworkers[21] demonstrated a nearly threefold increase in the adjusted odds of developing proteinuria among individuals with urine dipsticks positive for blood alone.[21] Other prospective studies from Asian countries have demonstrated rates of incident proteinuria of 10% to 11% among patients with pre-existing MH.[22,23] Recognizing that elevated urinary protein excretion is an established independent risk factor for all-cause and cardiovascular mortality and nonfatal cardiovascular and kidney disease,[24] the link between hematuria and the subsequent development of proteinuria may have significant clinical implications. This suggests that the finding of glomerular MH alone may not be as "benign" as previously thought.

Cancer of the bladder or upper GU tract is perhaps the most worrisome cause of MH. It is estimated that approximately 2.4% of the population will be diagnosed with bladder cancer in their lifetime, with an overall 5-year survival rate of 77.4%.[25] Documented risk factors for developing bladder cancer include smoking history, exposure to diesel fuel and fumes, aromatic amines, dry cleaning fluids, radioactive materials and arsenic, or alkylating agents, such as cyclophosphamide, and reduced DNA repair capacity.[26,27] One study reported that longer duration of time between recognition of hematuria and cancer diagnosis among individuals aged 66 years or older is an independent predictor of death from bladder cancer, although the nature of hematuria in this study (gross vs microscopic) was not specified.[28] Cancer of the kidney and renal pelvis is somewhat less common than bladder cancer, although the 5-year survival is worse.[29]

In addressing the association between MH and GU malignancy, the 2012 AUA guideline cites a 2.6% malignancy rate among 3762 individuals enrolled in population screening studies. In addition, it reports that 4.0% of 9206 patients referred for initial workup and 2.8% of 1475 patients requiring additional workup for MH were found to have malignancy.[1] The most recent estimates of GU cancer rates among patients with MH range from 0.68% to 15.7%, with the highest estimates coming from a study in which the authors acknowledge that the higher than expected rate was likely related to local referral patterns.[30-34] In another study, urologists at Kaiser Permanente reported on 4414 adults referred for evaluation of asymptomatic MH from 2009 to 2011.[31] GU cancer was found in 3.4% of subjects, including 100 cases of bladder cancer and 11 cases of kidney cancer. Using these data, the authors developed a "Hematuria Risk Index" to identify significant predictors of urologic malignancy. Although the findings of previous gross hematuria and age 50 years or older had the highest predictive value, smoking history, male sex, and greater than 25 RBC/hpf on recent urinalysis were also statistically significant risk factors.

EVALUATION STRATEGIES

Urine microscopy frequently confirms the presence of RBCs in the urine. Because dipstick reagents are not specific for blood and may turn positive in the presence of hemoglobin, myoglobin, concentrated urine, and vigorous physical activity, microscopic examination of urine is essential on finding a dipstick positive for blood.[9] In addition to confirming the presence of RBCs, microscopy also identifies cell morphology. The specific findings of dysmorphic RBCs (particularly acanthocytes) or RBC casts on microscopy,