MAYO CLINIC

EDITORIAL

February 2013
Volume 88
Number 2

MAYO CLINIC
PROCEEDINGS

Proper Evaluation of Asymptomatic Microscopic Hematuria in the Era of Evidence-Based Medicine—Progress Is Being Made

See also page 129

Urinalysis is one of the most commonly performed tests in clinical practice. In addition to being a part of the diagnostic evaluation of symptomatic patients or for monitoring of known renal or urological disease, urinalysis is considered an important component of the initial laboratory evaluation of asymptomatic patients with common health disorders such as essential hypertension and diabetes mellitus. Moreover, it is often performed as a broad screening test in asymptomatic, healthy adults. The prevalence of microhematuria in asymptomatic patients is common and ranges as high as 21%, with variation in estimates based on the distribution of age and sex in the populations studied.[1] According to current guidelines of the American Urological Association (AUA),[2] once benign causes (eg, infection, menstruation, medical renal disease, or trauma) have been excluded, patients with asymptomatic microhematuria should undergo a urological evaluation that includes imaging with multiphase computed tomography with and without intravenous contrast medium, and patients 35 years and older or younger patients with risk factors for urinary tract cancer should undergo a cystoscopic examination. However, the strength of evidence supporting this recommendation is low (evidence strength grade C), and studies suggest that primary care physicians do not refer patients with asymptomatic microhematuria for urological evaluation according to these guideline recommendations.[3,4]

Poor referral rates are probably in large part due to awareness that the frequency of serious urological disease in patients with asymptomatic microhematuria is low—malignant origins range from 0.5% to 5.0%, with lower estimates observed in population-based samples and higher estimates in referral samples.[2,5,6] Thus, it is recognized that by following the current guidelines, many patients will undergo costly diagnostic procedures and be exposed to potential test-related morbidity without any benefit. Many primary care physicians struggle with decision making, being aware of the low risk of malignant disease on one hand but on the other hand not wanting to miss a chance for early diagnosis of a potentially lethal condition. Thus, there is a clear need for quality studies to better inform recommendations for the evaluation of patients with asymptomatic microhematuria. This need was acknowledged by the AUA in their most recent guideline report, in which they noted that due to research priorities and limited finances, prospective randomized studies in this area are unlikely to be forthcoming and that high-quality single-institution or collaborative cohort studies will be important to better inform decision making for the evaluation of asymptomatic microhematuria.[2]

In this issue of *Mayo Clinic Proceedings*, Loo et al[7] report the results of a prospective cohort study of patients evaluated for asymptomatic microhematuria by urologists within the Kaiser Permanente managed care organization. All study patients underwent the recommended workup with both imaging studies and cystoscopy and were subsequently followed up passively (through electronic medical records) for the development of urothelial or renal cancer. Risk factors for malignant tumors were identified in a test cohort, and each identified risk factor was assigned a point value based on parameter estimates from a logistic regression model to create a Hematuria Risk Index. The

index was then further assessed in a validation cohort to identify patients with asymptomatic microhematuria at high or low risk for urinary tract cancer. The most informative risk factors in the Hematuria Risk Index were age 50 years or older and a history of recent (within 6 months) gross hematuria, whereas less informative risk factors were a history of smoking, degree of microhematuria, and male sex. The Hematuria Risk Index identified 32% of the validation sample as having a low risk for malignant disease, and cancer was detected in only 0.2% of this group. In contrast, 14% of the sample was labeled as having a high risk for malignant disease, and cancer was detected in 11.1% of this group. The authors concluded that use of the Hematuria Risk Index may significantly reduce the number of unnecessary workups in asymptomatic patients with microhematuria while identifying a high-risk subset that should undergo immediate evaluation. This study represents an important step in the development of evidence-based recommendations for appropriate and cost-effective evaluation of patients with asymptomatic microhematuria.

Importantly, not all recognized risk factors for urinary tract cancer were assessed in this study. Risk factors not identified in this cohort study include occupational exposure to chemicals such as benzenes or aromatic amines, history of analgesic abuse, previous pelvic irradiation, or prior treatment with certain chemotherapeutic agents.[2] Identification of these additional risk factors, although not common in the general population, is highly relevant in individual patients and emphasizes the important clinical point that use of a "risk score" as proposed in this study may be helpful but should only be used as part of a broader assessment of risk in the individual patient. The importance of obtaining a thorough history in patients with microhematuria is emphasized by the observation in this study that the recent occurrence of gross hematuria, a well-recognized important risk factor for urinary tract cancer, was frequently not noted by the primary care physician.

It is always important to distinguish patients with gross hematuria from those with microhematuria because, in contrast to the infrequent occurrence of cancer in patients with asymptomatic microhematuria, up to 19% of those with gross hematuria will be found to have an underlying urinary tract malignant neoplasm.[8] Therefore, it is recommended that all patients with gross hematuria undergo a urological workup. Indeed, in the present report, Loo et al[7] confirmed that a history of recent gross hematuria is an important risk factor for urinary tract cancer because it was one of the two most important risk factors contributing to the Hematuria Risk Index. A history of recent gross hematuria was common in the study cohorts (14.4% in the test cohort and 27.8% in the validation cohort). How well the hematuria index would have performed if this subset was excluded and only patients with isolated microhematuria were assessed is uncertain.

Also of interest in the report by Loo et al[7] is the observation that a history of smoking was only a minor risk factor for urinary tract malignant disease. Previous studies have shown that a history of cigarette smoking is the most potent environmental risk factor for bladder cancer. A recent study by Freedman et al[9] observed a 4-fold increase in risk of bladder cancer in smokers compared to those who never smoked, with a population-attributable risk for bladder cancer of 50% in men and 52% in women. Such data regarding the risk imposed by smoking emphasizes the need, as Loo et al noted, to assess the diagnostic accuracy of the Hematuria Risk Index in other populations that may differ in smoking habits, racial makeup, or exposure to other potential carcinogens before making generalizations regarding the overall value of the index in clinical practice.

Studies to better inform decision making in this area are even more important given the recent change in the definition of microhematuria by the AUA. In previous AUA guidelines, microhematuria was defined as the finding of 3 or more red blood cells per high-powered field on at least 2 of 3 properly collected urine specimens. In the most recent AUA statement,[2] microhematuria is now defined by a single positive urinalysis result, potentially markedly increasing the number of patients who would be candidates for urological evaluation. For example, in the study by Loo et al,[7] redefining microhematuria based on findings of a single urinalysis would have potentially increased the number of patients eligible for further workup by up to 34%.

Mayo Clin Proc. ■ February 2013;88(2):123-125 ■ http://dx.doi.org/10.1016/j.mayocp.2012.12.006
www.mayoclinicproceedings.org

The mantra of the future is individualized medicine. In this regard, development of a Hematuria Risk Index is a potential valuable first step to better inform who among the many patients with asymptomatic microhematuria should undergo further diagnostic evaluation. Other efforts to better inform appropriate referrals to urologists include the development of urinary biomarkers for urinary tract cancer. A recent study identified a panel of microRNAs with a high sensitivity for bladder cancer.[10] When applied to patients with hematuria, the panel would have found 94% of urothelial cancers and reduced the need for cystoscopy by 26%. Additionally, in a September 2012 report in *Mayo Clinic Proceedings*, Karnes et al[11] identified a multianalyte assay that stratified patients with hematuria into those at high and low risk for bladder cancer with a high degree of confidence. The report by Loo et al[7] in the current issue of *Mayo Clinic Proceedings* adds to a growing series of studies that hopefully will fulfill the promise of individualized medicine for the evaluation of patients with asymptomatic microhematuria.

Gary L. Schwartz, MD
Division of Nephrology and Hypertension
Mayo Clinic
Rochester, MN

Correspondence: Address to Gary L. Schwartz, MD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (gschwartz@mayo.edu).

REFERENCES

1. Grossfeld G, Wolf JS Jr, Litwan MS, et al. Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. *Am Fam Physician*. 2001;63(6):1145-1154.
2. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol*. 2012;188(6, suppl):2473-2481.
3. Nieder AM, Lotan Y, Nuss GR, et al. Are patients with hematuria appropriately referred to urology? a multi-institutional questionnaire based survey. *Urol Oncol*. 2010;28(5):500-503.
4. Elias K, Svatek RS, Gupta S, Ho R, Lotan Y. High-risk patients with hematuria are not evaluated according to guideline recommendations. *Cancer*. 2010;116(12):2954-2959.
5. Mohr DN, Offord KP, Owen RA, Melton LJ III. Asymptomatic microhematuria and urologic disease: a population-based study. *JAMA*. 1986;256(2):224-229.
6. Cohen RA, Brown RS. Microscopic hematuria. *N Engl J Med*. 2003;348(23):2330-2338.
7. Loo RK, Lieberman SF, Slezak JM, et al. Stratifying risk of urinary malignant tumors in patients with asymptomatic microscopic hematuria. *Mayo Clinic Proc*. 2013;88(2):129-138.
8. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. *J Urol*. 2000;163(2):524-527.
9. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA*. 2011;306(7):737-745.
10. Miah S, Dudziec E, Drayton RM, et al. An evaluation of urinary microRNA reveals a high sensitivity for bladder cancer. *Br J Cancer*. 2012;107(1):123-128.
11. Karnes RJ, Fernandez CA, Shuber AP. A noninvasive multianalyte urine-based diagnostic assay for urothelial cancer of the bladder in the evaluation of hematuria. *Mayo Clin Proc*. 2012;87(9):835-842.