Nephrology: 2. Evaluation of asymptomatic hematuria and proteinuria in adult primary care

Andrew A. House, Daniel C. Cattran

Case 1

Ms. M, a 27-year-old woman with a complaint of mild fatigue, is found to have a positive urinary dipstick test for hematuria. The patient does not have gross hematuria, voiding symptoms, renal colic or symptoms of systemic disease, such as infection or connective tissue disease. She is not currently experiencing menstrual bleeding. She has never been known to have hematuria, although she has experienced occasional lower urinary tract infections. There is no history of occupational exposure to carcinogens, and Ms. M has been a lifelong nonsmoker. The family history is unremarkable with respect to renal disease. Physical examination reveals a blood pressure of 110/70 mm Hg, no edema, rash or abdominal findings. Does Ms. M have hematuria? Is the source glomerular or nonglomerular? Is she likely to have a serious urinary tract pathology such as a malignancy? What investigations are needed to determine the need for referral and the urgency of referral?

Case 2

Mr. A, a 30-year-old man, is turned down for life insurance because of the presence of an unspecified amount of proteinuria. His past medical history is unremarkable, and he is not taking any medications. There is no history of diabetes or hypertension. His family history is negative for diabetes or renal diseases. At the time of assessment, Mr. A is a cigarette smoker but says that he does not consume alcohol or use recreational drugs. He has no voiding symptoms or anything suggestive of a systemic infectious or inflammatory condition. He was recently married and is employed as a locksmith. Physical examination reveals a fit male with a blood pressure of 125/76 mm Hg. The results of examination of his chest, abdomen and extremities are normal, and there is no edema, rash, lymphadenopathy or joint inflammation. Does Mr. A have serious renal disease? What investigations are needed to determine the nature and severity of the proteinuria?

Asymptomatic urinary abnormalities in adults are commonly encountered in primary care. Point prevalence estimates from population screening for hematuria range from < 1% in the first 3–4 decades of life to 13% for older individuals,[1–5] whereas proteinuria is less common.[2] The presence of microscopic hematuria or proteinuria may represent serious pathology in the kidneys or urinary tract, but preliminary evaluation can and should be initiated by the primary care practitioner, with subsequent management or referral, or both, guided by the findings of laboratory investigations. Hematuria and proteinuria often coexist but are discussed here as separate entities to allow the reader, in each case, to follow the predominant presenting feature to its conclusion. The suggestions that follow do not apply to gross hematuria, in which structural urinary tract abnormalities, infection, stones or malignancy merit prompt consideration.

Hematuria

Because reagent strips for urine hemoglobin cannot be used to distinguish readily between the presence of erythrocytes and free hemoglobin or myoglobin, the positive results of a dipstick test must be confirmed by microscopic examination.[6] Women may be susceptible to contamination of the urine by blood from menses or lesions of the reproductive tract, thus, these sources of blood loss must be considered in the history, the physical examination and in the timing of follow-up testing. Ideally, clean-catch midstream urine is collected first thing in the morning and examined within a few hours of collection. The first morning urine tends to be of lower pH and higher osmolality than at other times of day, which provides favourable conditions for the preservation of urinary erythrocytes.[7] The urine should be centrifuged and examined at low and high power for cells, crystals and other formed elements. The presence of 3 or more erythrocytes per high-power field in at least 2 of 3 urine samples is considered confirmatory and should prompt further investigation.[4,8–11] Infection should be considered as a potential cause of hematuria. Failure to confirm hematuria on repeat testing is reassuring, although some sources have recommended repeated tests over the following year to reduce the likelihood of occult disease.[4] The emergence of new urinary symptoms, the recurrence

of microscopic hematuria or the appearance of gross hematuria at any time should trigger reassessment.

If repeat testing confirms the presence of hematuria, the next step is to determine whether the source is glomerular or nonglomerular. Elements of the history and physical examination may be helpful, such as symptoms of systemic inflammatory disease or the presence of edema, hypertension or purpura that suggest a glomerular cause, whereas exposure to known occupational carcinogens such as aromatic amines or nitrosamines, a history of smoking or the use of certain Chinese herbs (aristolochic acid) or cyclophosphamide would increase the risk for uroepithelial malignancy.[12,13] Family history of nephrolithiasis or nephritis may also provide clues as to the cause.

Strong indicators of glomerular disease include the identification of urinary erythrocyte casts[6,9,10] or the presence of proteinuria on dipstick testing of 1+ or greater, which corresponds to a protein concentration of ≥ 3 g/L.[9,10] In this case, determination of levels of urea and creatinine and 24-hour urine protein excretion and creatinine clearance should be undertaken and consideration given to referral for nephrologic assessment.[14] The urgency of the referral can be gauged by the severity of renal dysfunction, rate of deterioration of function or degree of proteinuria. For example, it has been suggested that an increase in serum creatinine of more than 20% over a short period of time or a newly discovered creatinine level of above 300 μmol/L are indications for urgent referral.[14] Proteinuria in the nephrotic range (> 3.5 g/day) warrants prompt, though perhaps not urgent, attention. It must be remembered that a creatinine level above the upper limit of "normal" or more than 150 μmol/L represents the loss of at least 50% of renal function in most individuals, and considerably more than 50% in the elderly or small-framed patient. Where there is doubt concerning the timing of referral, the primary care practitioner should contact the consultant for advice.

For patients with no indicators of a glomerular cause, ultrasonography and urine cytology should be undertaken.[4] Individuals with African ancestry should be evaluated for sickle cell hemoglobinopathy. Intravenous pyelography may be of additional utility in patients at high risk of uroepithelial neoplasm.[15] New urine markers with greater sensitivity and specificity for the diagnosis of transitional cell bladder cancer compared with standard urine cytology are now available for the follow-up of patients with known bladder cancer, but their exact role in the diagnosis of new cases of malignancy remains to be defined.[8,16,17] Several studies have found the risk of urinary tract malignancy to be closely related to age and sex.[11,15] In one prospective study, 1034 asymptomatic adults (272 men, 762 women) with microscopic hematuria underwent extensive urologic investigation, yielding malignancy in 5.9% of men and 1.0% of women.[15] All cases of malignancy were found in subjects over 40 years of age. In another study of 1000 men aged 18–40 years, followed for a mean of 12.2 years, the cumulative incidence of hematuria on annual testing was 38.7%, but only one malignancy (transitional cell carcinoma of the bladder) was discovered in a subject who had a history of episodic gross hematuria.[3] A more recent study of 982 subjects (498 men, 484 women) with microscopic hematuria identified malignancy in 6.8% of men and 3.5% of women.[18] One malignancy (bladder) was identified in a male subject aged less than 40 years, out of 143 subjects less than 40 years of age. These observations have led to the recommendation of prompt referral for urologic assessment including cystoscopy or cystourethrography, or both, for individuals with asymptomatic microscopic hematuria aged over 40 years.[15] Such assessment would be appropriate in younger individuals with significant risk factors, positive urine cytology or the development of new symptoms such as dysuria, urgency or gross hematuria.

A number of individuals with asymptomatic microscopic hematuria will be found to have normal renal function, no proteinuria, calculi or malignancy and will, thus, remain without a specific diagnosis. Likely diagnoses in this remaining group include IgA nephropathy, thin glomerular basement membrane nephropathy, hypercalciuria or hyperuricosuria.[19–21] The prognosis of isolated microscopic hematuria is generally considered to be favourable. Yamagata and colleagues followed 432 such patients identified in a mass screening of 56 269 employees of Hitachi, Ltd., for a mean of 5.8 years. They observed spontaneous resolution of hematuria in 44.2% of cases, persistent hematuria without proteinuria in 43.7%, nephrolithiasis in 1.4% and development of proteinuria without azotemia in 10.6%.[2] It would, therefore, seem reasonable to follow these individuals with annual urinalysis and less frequent determination of serum creatinine, provided they remain free of symptoms, gross hematuria or significant proteinuria.

Case 1 revisited

In the case described here, apart from the history of urinary tract infections, there were no elements in the history or physical examination to suggest a source for the hematuria. Referring to the algorithm in Fig. 1 led the patient's practitioner to rule out infection and to seek microscopic confirmation of hematuria. Specifically, the physician arranged repeat urinalysis at a time when there was no menstrual bleeding, which confirmed the presence of numerous erythrocytes and also revealed dipstick-positive proteinuria. The results of the urine culture were negative.

The physician caring for Ms. M recognized the gravity of the proteinuria coupled with hematuria and ordered tests of urea and creatinine levels, both of which were elevated, and arranged for a timed urine collection for protein and creatinine clearance in addition to abdominal ultrasonography. The results of ultrasonography were unremarkable, timed urine collection revealed proteinuria in excess of 2 g per 24 hours, and creatinine clearance was about 30% of expected. Ms. M was referred without delay to a nephrologist who promptly arranged a renal biopsy.

If a glomerular cause of Ms. M's hematuria had seemed unlikely from the history, physical examination and analysis of the urine, the next step in the algorithm would have led to investigation for urinary tract pathology and consideration of referral for urologic assessment. Because Ms. M had a very low pretest likelihood of urinary tract malignancy and strong indicators for intrinsic renal disease were present, it was reasonable not to refer her for cystoscopy. She did undergo a renal biopsy, which revealed IgA nephritis and significant interstitial fibrosis.

Proteinuria

In primary care, proteinuria is often discovered as the result of a positive dipstick test, with the degree of proteinuria indicated by a change in colour of the reagent, ranging from trace (0.5–2 g/L) to 4+ (> 20 g/L). A value of 1+ or greater corresponds to a protein concentration of at least 3 g/L and is generally considered to be "positive." Very alkaline or concentrated urine may result in an overestimate of the daily excretion of protein, thus a positive dipstick test does not always correspond to significant proteinuria as measured by timed collection. Standard dipstick testing lacks the sensitivity to detect microalbuminuria (defined as 30–300 mg albumin excretion per 24 hours) and is thus not appropriate for screening diabetic patients, who may have incipient diabetic nephropathy in the absence of dipstick-positive proteinuria.

Asymptomatic proteinuria may be the first manifestation of significant renal or systemic disease, although for many individuals it is a benign, transient phenomenon. In a review of population-based studies screening for asymptomatic proteinuria, a minority of proteinuric subjects were found to have serious urinary tract or renal abnormalities.[22] The presence (or absence) of protein in the urine depends upon the following: the amount of filtered protein, which in turn depends upon protein concentration in the plasma and the glomerular filtration rate; the permeability of the glomerular basement membrane; and the ability of the proximal tubule to metabolize and reabsorb any filtered

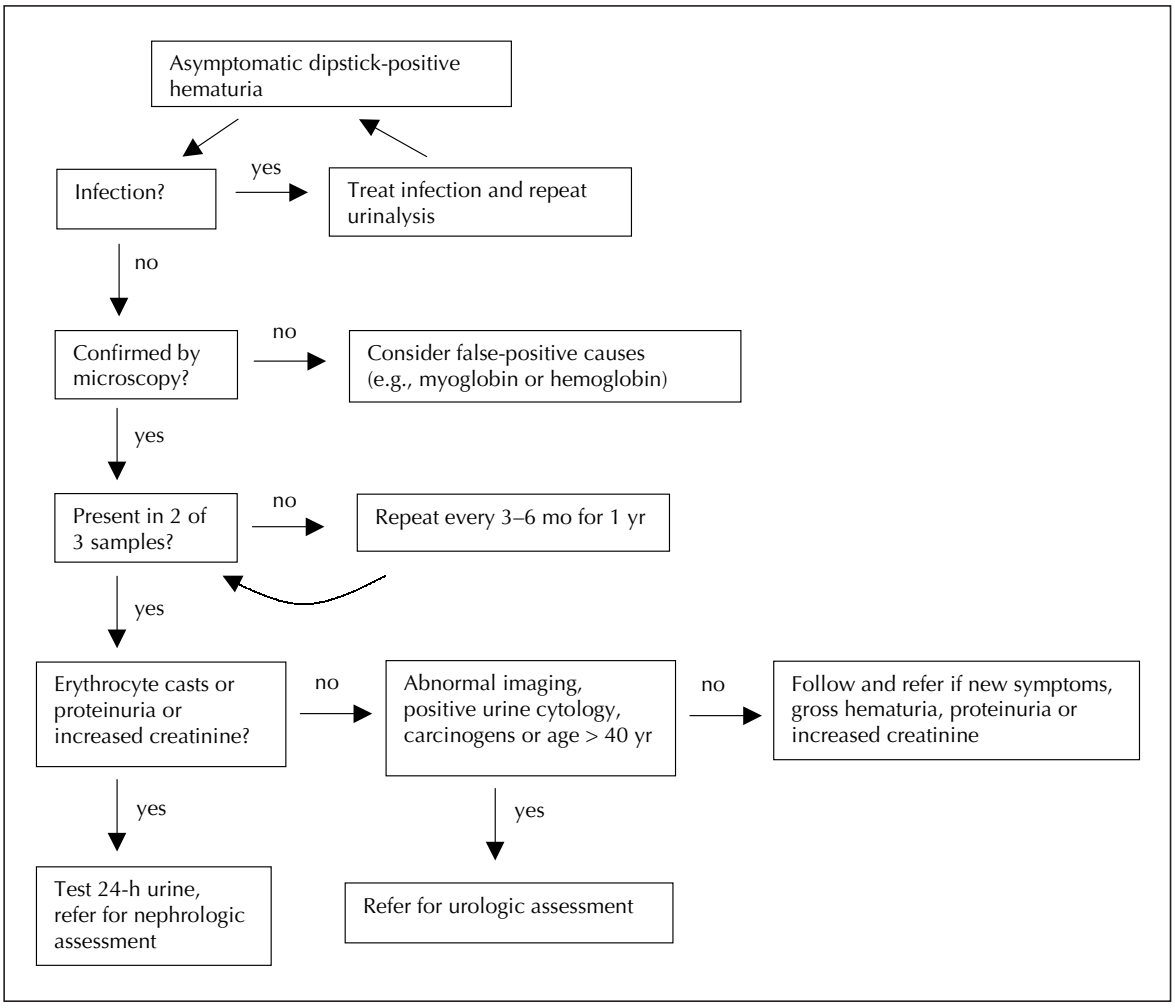

Fig. 1: Algorithm for the suggested investigation and management of asymptomatic microscopic hematuria in adult patients.

proteins. When these mechanisms are intact, the normal excretion of protein should be less than 0.15 g per day.[10,23,24]

Proteinuria is often classified as functional, glomerular, tubular or overflow, and this distinction can often be made by history-taking, physical examination and relatively simple testing.[10,23,24] Functional proteinuria describes the transient increase in protein excretion that accompanies changes in glomerular hemodynamics that may occur with exercise or fever. Almost one-quarter of the proteinuric subjects in the Hitachi cohort experienced only transient proteinuria with no adverse sequelae.[2] A unique category of functional proteinuria that appears typically in individuals less than 30 years of age is postural or orthostatic proteinuria, whereby individuals have no proteinuria in the early morning (provided they have been recumbent overnight) and significant proteinuria after standing for a length of time. Practitioners who suspect the presence of orthostatic proteinuria can confirm this by having their patient void herself or himself before retiring for the night and provide a specimen for analysis immediately upon rising in the morning, followed by a sample later in the day for comparison. More sophisticated timed samples may be necessary. Functional proteinuria generally follows a benign course, as does orthostatic proteinuria, whereby most individuals experience spontaneous resolution of proteinuria and no serious sequelae after many years of follow-up.[23,25]

If proteinuria is persistent over 2 or more samples, the next step, as shown in the algorithm in Fig. 2, is to quantify the amount of protein excretion by a timed (usually 24-hour) collection. If timed urine collection confirms that protein excretion is above 0.15 g/day, then the nature of the proteinuria may be determined by the history, physical examination and some basic investigations, which can include ultrasonography of the kidneys and measurement of levels of urea, creatinine and fasting glucose. Urinalysis is used to detect hematuria or infection. The presence of hematuria or urinary erythrocyte casts strongly suggests glomerular disease, and the practitioner should consider referral for nephrologic assessment. History-taking should focus on potential systemic illness, such as diabetes, multi-

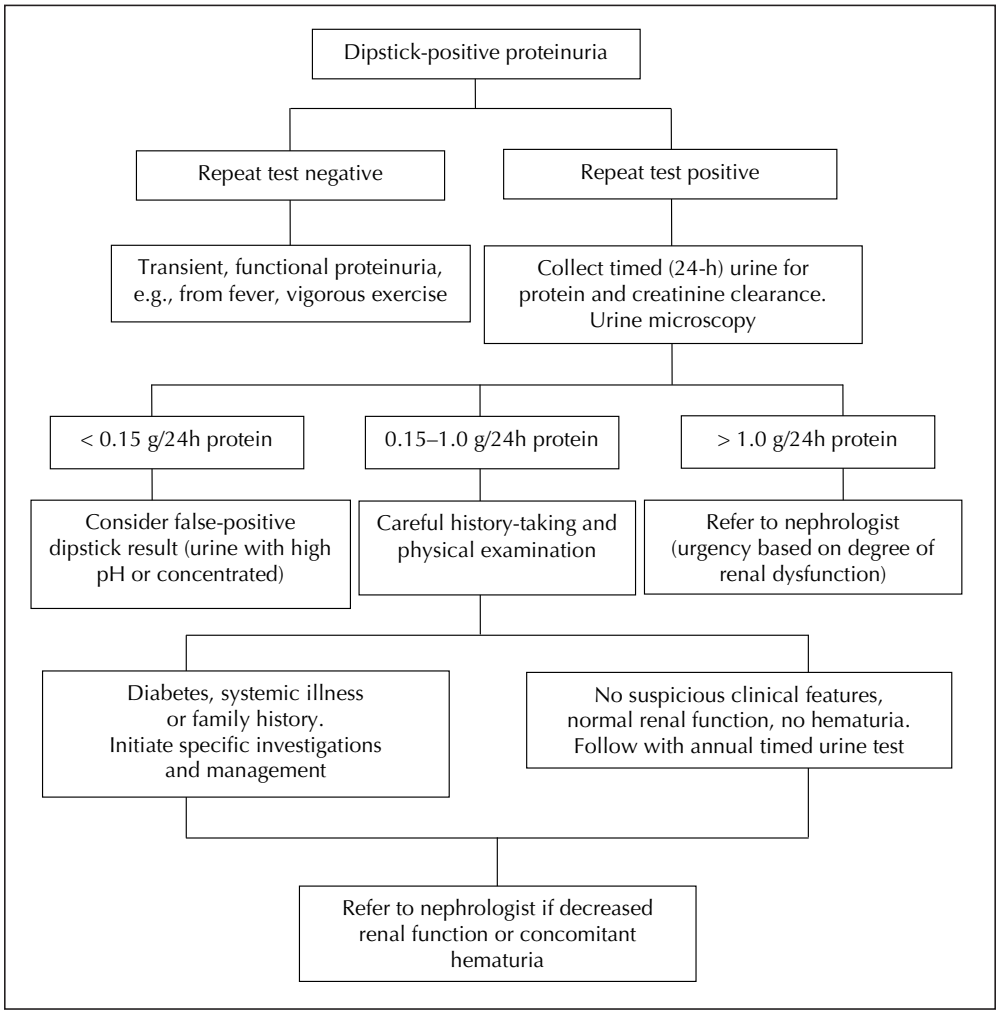

Fig. 2: Algorithm for the suggested investigation and management of dipstick-positive proteinuria in adult patients.

ple myeloma, connective tissue disease, malignancy, vasculitis, chronic infection or primary renal disease, and should include a careful medication history and family history. The physical examination includes careful assessment of blood pressure and volume status while searching for manifestations of systemic illness.

To better categorize proteinuria, the primary care practitioner may find urine protein electrophoresis to be helpful. Proteinuria in the nephrotic range (> 3.5 g/day) is often glomerular in nature and consists mostly of albumin, whereas lower amounts of protein may be glomerular or tubular. The electrophoretic pattern of tubular proteinuria is predominantly that of globulins with multiple peaks.[24] "Overflow" proteinuria, which can occur with light chain overproduction from multiple myeloma, often appears as a single electrophoretic peak. Referral for further investigations or management, or both, of persistent proteinuria is based on the results of the investigations described earlier, with urgency of referral determined by the severity of renal dysfunction, the rate of deterioration or the degree of proteinuria, as outlined in the section on hematuria.

Key points

- Microscopic hematuria should be confirmed by repeat testing and urine microscopy
- The coexistence of microscopic hematuria with urinary erythrocyte casts or dipstick-positive proteinuria strongly suggests glomerular disease
- The risk of serious urinary tract pathology including malignancy as a cause of microhematuria increases sharply in individuals over the age of 40 years
- Standard dipstick testing is not sensitive enough for the detection of microalbuminuria and incipient diabetic nephropathy
- Proteinuria is often transient and benign in nature, but fixed proteinuria may represent serious kidney disease
- Serum creatinine levels above 150 µmol/L or above the upper limit of "normal" may represent significant loss of kidney function

Asymptomatic isolated proteinuria for which no specific diagnosis is discovered tends to run a fairly benign course, although its presence may be a harbinger of serious renal disease. In the study by Yamagata and colleagues, 177 of 56 269 screened individuals had isolated proteinuria; of these individuals, 7.9% had orthostatic proteinuria, 2.2% had chronic renal insufficiency at the outset and 4.5% were diagnosed with a variety of other conditions, including diabetic nephropathy and polycystic kidney disease. The remaining 151 patients were undiagnosed at presentation. Almost 25% of these patients had resolution of their proteinuria, most remained stable, but 10% subsequently developed deterioration of renal function over a mean follow-up period of 8 years.[2] In the absence of a diagnosis, it would seem reasonable to simply follow the mildly proteinuric patient with intermittent determinations of both renal function and protein excretion rate. Consideration should be given to treatment with an angiotensin-converting-enzyme inhibitor or angiotensin-II receptor blocker in select patients, such as those with diabetes, hypertension or progressive nephropathies.[26–31] The role of such treatment in nondiabetic individuals with normal renal function and blood pressure has not yet been established.

Case 2 revisited

After being denied insurance, Mr. A sought the attention of his family physician, who confirmed the presence of persistent proteinuria, ranging from 1+ to 3+, by the dipstick test on several occasions, with no hematuria. Timed urine collection confirmed the excretion of 700 mg of protein daily, with normal creatinine clearance. The history and physical examination provided no clues as to the cause of the proteinuria. The results of a complete blood count and biochemistry, including fasting glucose, were unremarkable. No structural abnormalities were revealed by ultrasonography.

The physician caring for Mr. A was concerned about the degree of proteinuria but reassured by the lack of systemic disease and the normal creatinine clearance. The patient was referred on a nonurgent basis to a nephrologist who performed some serologic tests for various secondary causes of proteinuria. Given the modest amount of protein excretion and the stable renal function, the nephrologist elected to forgo a renal biopsy and suggested management with annual timed testing of urine and serum creatinine levels.

Comment

The discovery of asymptomatic microscopic hematuria or proteinuria, or both, is common in general practice. With a careful history-taking, physical examination and readily available radiologic and laboratory testing, the primary care practitioner will be able to determine both the need and urgency for referral for further investigation and management. The algorithms suggested in this paper provide a relatively straightforward and logical approach to these problems and allow the streamlining of referrals for patients for whom further diagnostic or therapeutic interventions are required.

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Dr. House is with the Division of Nephrology, Department of Medicine, University of Western Ontario, London Health Sciences Centre — University Campus, London, Ont. Dr. Cattran is with the Division of Nephrology, Department of Medicine, University of Toronto, Toronto General Hospital, Toronto, Ont.

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Correspondence to: *Dr. Andrew A. House, Division of Nephrology, London Health Sciences Centre, 339 Windermere Rd., PO Box 5339, Station B, London ON N6A 5A5; fax 519 663-8808; Andrew.House@lhsc.on.ca*

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