

Microscopic Haematuria

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A 30 year old man is referred for a medical check up before taking a life insurance policy. He is asymptomatic, gives no relevant history, is on no treatment and physical examination is unremarkable. Routine dip-stick analysis of a mid-stream specimen of urine reveals traces of blood. What is to be done?

Introduction

This is an all too common problem. The causes of microscopic haematuria range from minor to life threatening. They vary with age. Not all cases require urgent and in-depth investigation. On the other hand one must be careful not to miss conditions, particularly neoplasia, where early diagnosis and management can make a real difference to outcomes and to quality of patient life.¹ Patients with glomerular disease also have better outcomes when referred early for specialist management.²

Definitions and Concepts

Many subjects will have microscopic haematuria at some stage in their lives. In the overall population, the point prevalence is around 4%.³ Grossfield and Carroll carried out a metaanalysis in 1998 and put the overall incidence at 0.2 to 21.1%. A relatively high proportion were found to have a specific cause, and of these 3.4-56% had moderately or highly significant lesions at the time of diagnosis.¹

The American Urological Association (AUA) Best Practice Policy Panel on Asymptomatic Microscopic Haematuria defines microscopic haematuria as three or more red blood cells (RBCs) per high power microscopic field (HPF) of urinary sediment from two or three properly collected urinalysis specimens.⁴ Most individuals will have 1 RBC or less per HPF or per ml. This is equivalent to a loss of 1-10 RBCs per nephron daily. These cells are mostly dysmorphic. 5 mls. of blood per litre or 25,000 RBCs per ml will produce visible or gross haematuria, and twice this amount will produce persistent gross haematuria. Dip-sticks detect blood from lysed RBC's, which lyse more easily in alkaline urine. Their active reagent is usually orthotoluidine. This also

gives a positive test in intravascular haemolysis with haemoglobinuria, in myoglobinuria and when there is infection with certain peroxidase producing bacteria. Many healthy individuals with urinary RBC losses at the upper limits of normal will have positive tests at some time in their lives. False negative tests occur with urine containing high concentrations of ascorbic acid. Dip-stick analysis is 100% sensitive, but only 62% specific. Hence, a persistently positive test must always be corroborated by urinalysis and microscopy.⁵ Table 1 summarises the prevalence of microscopic haematuria by age.

Causes

The two questions to be kept in mind when investigating microscopic haematuria are:

1. Is the haematuria glomerular, non-glomerular (parenchymal) or extrarenal in origin?
2. Depending on the patient's age, what is the main differential diagnosis?⁶

It is worth remembering that diseases and lesions of the urinary tract do not automatically cause haematuria, and this is often intermittent. Sugimura et al (2001) noted haematuria (microscopic or gross) in only 35% of 113 patients with renal cell carcinoma (RCC), while 94% of 236 patients with urothelial malignancies had haematuria at some stage. Of 823 patients with asymptomatic microscopic haematuria only 2.1% had urothelial malignancies and only 0.2% had RCC. However, of those aged over 50 years 6.2% had urothelial malignancies.⁷ Of about 100 young male military recruits investigated for

Table 1: Prevalence of microscopic haematuria by age. (Adapted from "Oxford Textbook of Clinical Nephrology"; 2nd Edition).⁵

Age Category	Prevalence
children < 12 years	1-4%
Young Males 18-33 years (Military recruits)	5.2%
Older Adults > 50 years	4-18% males; 14% females
Elderly > 75 years	13% males; 9% females

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asymptomatic microscopic haematuria by Sparwasser *et al* in 1994, 31.2 % had pathology and this was almost equally divided between glomerular disease (16.5% and most commonly IgA Nephropathy), and urothelial disease, of which only 2 had urothelial carcinomas.⁸

By far the greatest cause at all ages is infection of the urinary tract, followed by urolithiasis. A great age divide thus emerges; with those over 50 years having a higher incidence of urothelial disease and those of a younger age being less likely to have serious conditions and these being predominantly glomerular in origin.^{5,6} Small children below the age of three represent a special category where glomerular causes predominate but with Wilm's tumour, congenital abnormalities of the genitourinary tract and rhabdomyosarcoma of the bladder must be kept in mind.⁹ Table 2 lists the causes of microscopic haematuria.

Management

One must confirm that microscopic haematuria is really present by repeating dip-stick urine analysis once or twice, always using a clean-catch mid-stream specimen. Women of reproductive age should produce their sample before or several days after their menses. If the presence of microscopic haematuria is corroborated, one should immediately perform a formal urine analysis and microscopy on a fresh, early morning unspun and acidic urine sample. A Fuchs-Rosenthal counting chamber is used, ideally utilising phase-contrast microscopy.⁵ If bacteria are present, a urine culture is essential.¹⁰ It is important that when submitting urine to a laboratory, transportation times should be kept as short as possible. It is essential to take a full history with particular attention to symptoms, present and past history of diabetes, hypertension,

Table 2: Causes of Microscopic Haematuria (Adapted from the "Oxford Textbook of Clinical Nephrology" 2nd Edition, and "Primer on Kidney Diseases" 2nd Edition).^{5,6}

A. Glomerular

- Proliferative Glomerulopathies:
 1. Primary (IgA Nephropathy, Postinfective, Mesangiocapillary, Rapidly Progressive/Crescentic)
 2. Secondary (SLE, Anti glomerular basement membrane disease, systemic vasculitis, associated with bacteraemia eg SBE, associated with Hepatitis B and C, Essential Mixed Cryoglobulinaemia).
- Non-proliferative Glomerulopathies: (Minimal Change, Focal Segmental Glomerulosclerosis, Membranous, Haemolytic Uraemic Syndrome)
- Familial Glomerular Disease: (Alport's, Thin glomerular basement membrane disease, Fabry's disease, Nail-patella syndrome)

B. Non-glomerular

- Neoplasia (RCC, Wilm's tumour, Benign cysts, Angiomyolipoma of Tuberous Sclerosis, Multiple Myeloma)
- Vascular (Renal infarction, Renal vein thrombosis, Malignant hypertension, Arteriovenous malformation, Loin-pain Haematuria Syndrome)
- Metabolic (Hypercalcuria, Hyperoxaluria, Hyperuricosuria, Cystinuria)
- Familial (Autosomal dominant polycystic kidney disease, Medullary cystic disease, Medullary sponge kidney)
- Papillary Necrosis (Analgesia, Infection, Diabetes, Obstruction, Sickle cell anaemia and trait, Tuberculosis, Ankylosing Spondylitis, Alcohol Abuse)
- Hydronephrosis (All causes)
- Drug Induced (NSAID's, Aminoglycosides)
- Trauma (Renal and extrarenal; including exercise induced haemolysis as in "Jogger's Haematuria")

C. Extrarenal

- Urolithiasis
- Urothelial neoplasia
- Prostatic Adenocarcinoma
- Benign Prostatic Hypertrophy (BPH)
- Infective (Bacterial, Chlamydial, Fungal, Tuberculosis, Schistosomiasis)
- Drug Induced (Cyclophosphamide, Anticoagulants)
- Trauma to Lower Urinary Tract and Genitalia.
- Genital Bleeding.
- Factitious (Deliberate addition of blood to urine sample)

SLE – systemic lupus erythematosus; SBE – subacute bacterial endocarditis; NSAIDS – non-steroidal anti-inflammatory drugs; RCC – renal cell carcinoma

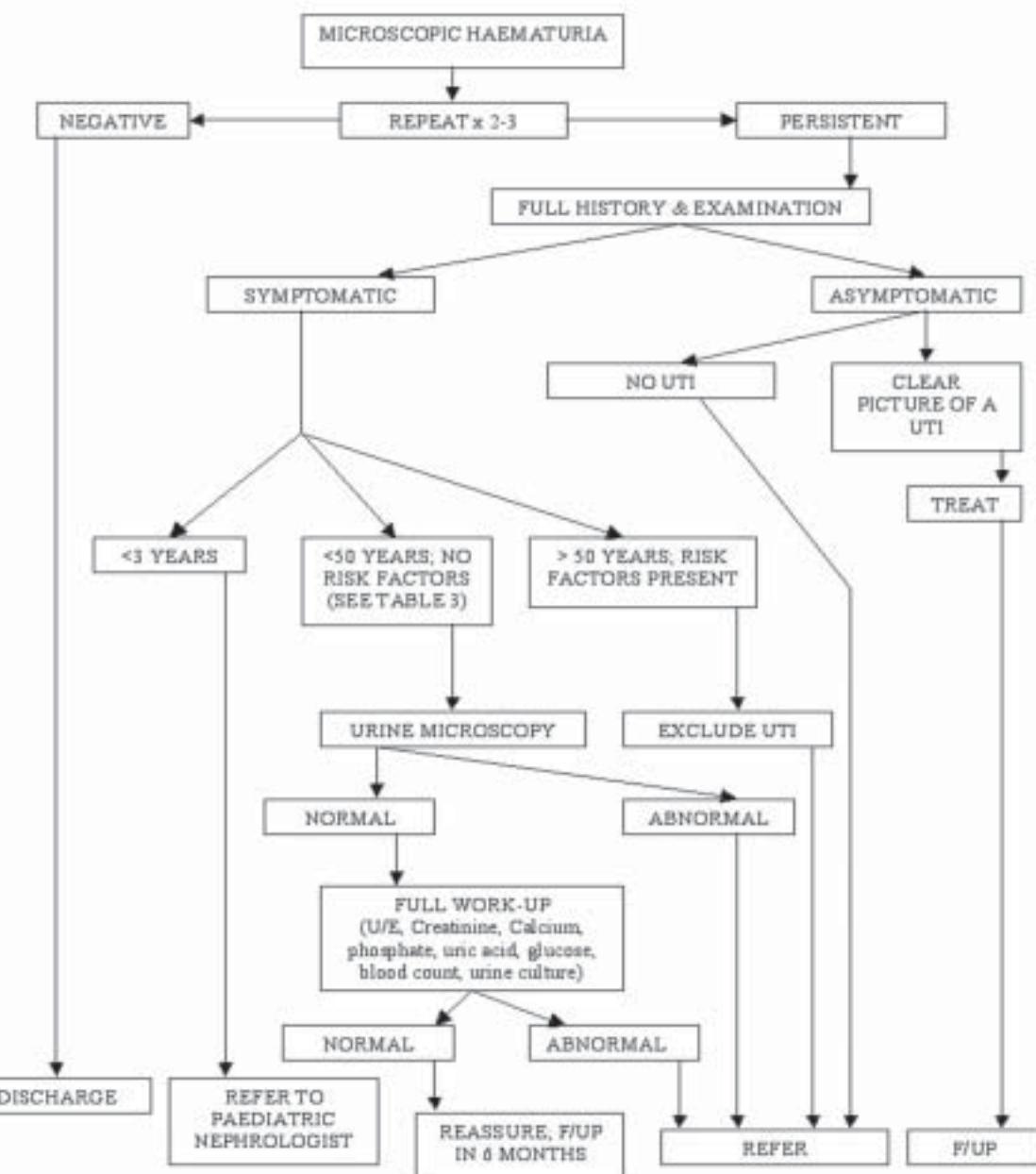
documented nephrological and urological problems; family history; medications (including analgesics, anticoagulants, over-the-counter and herbal preparations) and social and occupational history. A full physical examination must be performed, including blood-pressure measurement, fundoscopy, a rectal examination and examination of the external genitalia.

When to Refer?

A majority of positively screening subjects will not have major pathology. Chow *et al* (2004) followed 90 consecutive

patients with isolated microscopic haematuria between 1985 and 1996. The median follow-up time was 5.2 years. 17% of these had complete resolution of the problem. 13% developed hypertension and 11% developed proteinuria. Only one patient developed a malignancy, and another one went on to end-stage renal failure. Predictors for a poor outcome at start of follow-up were proteinuria, diminished glomerular filtration rate and hyperuricaemia.¹¹ Eardley *et al* (2004) carried out a retrospective study of a series of patients who underwent renal biopsy for microscopic haematuria and compared those without albuminuria with patients who had

Figure 1: Algorithm for the management of microscopic haematuria



Key: UTI – urinary tract infection; U/E – urea and electrolytes

Table 3: Markers of Increased Risk of Significant Pathology in Patients with Microscopic Haematuria

1. Those over 50 years
2. Children below 3 years
3. Presence of gross haematuria at any stage (unless already investigated)
4. Past history of renal disease
5. Proteinuria (including microalbuminuria)
6. Presence of diabetes and/or hypertension of more than 3 year's duration (even if well controlled)
7. Family history of renal disease
8. Presence of pain or systemic symptoms
9. Smokers (because of association with bladder cancer), occupational exposure to chemicals, history of analgesic abuse or use of herb remedies.
10. An abnormal urine microscopy, unless this is clearly due to a lower UTI

UTI – urinary tract infection

micro- or macro-albuminuria. It was noted that the latter had a significantly higher incidence of severe glomerular disease and significantly worse outcomes.¹² Microalbuminuria is an independent marker for an increased risk of cardiac events.¹³ Not all glomerular disease automatically produces microscopic haematuria, especially if secondary to systemic illness such as diabetes and hypertension.¹⁴

There is general agreement that patients over 50 years of age should be referred for urological assessment.¹⁵ It thus transpires that certain categories of patients are more "at risk" of having significant pathology (Table 3). These should be referred for specialist assessment, with age, symptoms and clinical findings guiding one to refer to a urologist or to a nephrologist. Asymptomatic patients who do not fall within the high risk category and who have a normal urine microscopy can be investigated and followed up at primary care level with full blood count, urea, electrolytes and creatinine, blood glucose, calcium, uric acid and coagulation screen. Where the findings can be reasonably explained away by the presence of a lower urinary tract infection (UTI), this can be similarly investigated, treated and followed up. Figure 1 is an algorithm for the management of this clinical problem.

Special Investigations

One should proceed to a straight penetrated X-ray of the abdomen (KUB), renal ultrasonography, and in selected patients, intravenous urography and computerized tomography of the urinary tract. All patients with a history of gross haematuria, and those with microscopic haematuria aged over 50, require flexible cystourethroscopy. In children, invasive investigations and radiation hazards should be kept to a minimum.¹⁶

The role of renal biopsy is controversial and yields very little information when there is asymptomatic haematuria or microscopic haematuria with low-grade haematuria. It is required where there is significant proteinuria (over 0.5-1.0g daily) or impaired renal function besides microscopic haematuria.¹⁷

In Conclusion

1. Microscopic haematuria is common.
2. Not all patients require specialist referral but those at risk should be referred.
3. Patients aged over 50 years have a greater likelihood of urological problems, while those below 40 years have a much lower risk of problems, with these tending to be glomerular.

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