Haematuria 2: imaging investigations, management and follow up

Haematuria is a common complaint presenting to doctors in both primary and secondary care. It can be a sign of underlying urinary tract malignancy. Appropriate investigation and management should follow evidence-based practice and recognized guidelines, and subsequently lead to a rapid diagnosis.

Haematuria can result in considerable patient anxiety and distress. The investigation and management of this common urological entity should be familiar to all doctors. The primary goal of investigation should be to exclude underlying malignancy. This second of two articles discusses the rationale of imaging investigations. The principles of management are considered along with the follow up of patients with negative investigations.

Imaging

Different imaging modalities vary in their sensitivity for detecting different pathology. The modality chosen is based upon its diagnostic strengths balanced against the risks of the investigation (e.g. radiation, contrast reaction), availability and expertise to interpret image findings. The primary aim of imaging is to assess the presence of urinary tract malignancy. There can be a wide range in local policy. In many centres ultrasound and plain abdominal radiograph of the kidneys, ureter and bladder (KUB) are the initial investigations. If negative, intravenous urography (IVU) is indicated in patients with persistent microscopic haematuria, or in patients over 40 years of age with microscopic haematuria (European Commission Directorate-General for the Environment, 2001).

Ultrasound

Ultrasound is excellent at detecting and characterizing renal cystic masses. It is also good at assessing renal morphology, structure and vasculature, and detecting hydronephrosis. It can assess bladder wall morphology, detect large bladder tumours and assess bladder emptying. However, ultrasound is less sensitive than IVU in diagnosing urothelial tumours (Grossfeld et al, 2001). It also has a lower sensitivity for detecting renal tumours <3 cm in size. Compared to computed tomography (CT), the sensitivity and specificity of ultrasound for detecting renal masses between 2 and 3 cm is 82% and 91% respectively (Brehmer, 2002). A study of 1930 patients over 3.5 years by Khadra et al (2000) showed that 43% of tumours would have been missed if ultrasound had been used alone. The sensitivity for detecting calculi is even lower, ranging from 37–64% and this is even poorer when compared with non-contrast helical CT as the reference standard, with a sensitivity of 24% and a specificity of 90% (Fowler et al, 2002). Stones in the pelvicalyceal system can only be reliably identified if they are >5 mm in size (Sandhu et al, 2003).

The advantages of ultrasound include that it is non-ionizing, safe, easy to use, inexpensive, portable, widely available and requires no prior patient preparation. It is the investigation of choice in pregnant women. The drawback of ultrasound is that it is very much operator dependent and the spatial resolution of images is poor compared to CT.

Intravenous urography

Compared to ultrasound, the IVU is better at detecting transitional cell carcinoma, which usually manifests as a filling defect in the intrarenal collecting system, pelvis and ureter. It has limited sensitivity in detecting small renal masses 2–3 cm and <2 cm in diameter (sensitivity 52% and 21% respectively) (Brehmer, 2002). It cannot distinguish solid from cystic masses, which require further evaluation with ultrasound, CT or magnetic resonance imaging (MRI). Ultrasound or IVU on its own is likely to miss upper urinary tract transitional cell carcinomas (Khadra et al, 2000). The detection rate is highest when both investigations are performed.

The IVU has a lower cost and radiation dose compared to CT. However, the radiation dose is significant (3–4.5 mSV) and equivalent to >150 chest X-rays. It takes longer to perform than CT or ultrasound. Adverse reactions caused by contrast media, such as vomiting or urticaria, may occur in up to 4% of patients, with a smaller proportion developing an anaphylactic reaction which can be fatal. Contrast cannot be used in patients with renal failure. Diabetic patients on metformin must stop taking metformin for 48 hours after the IVU to

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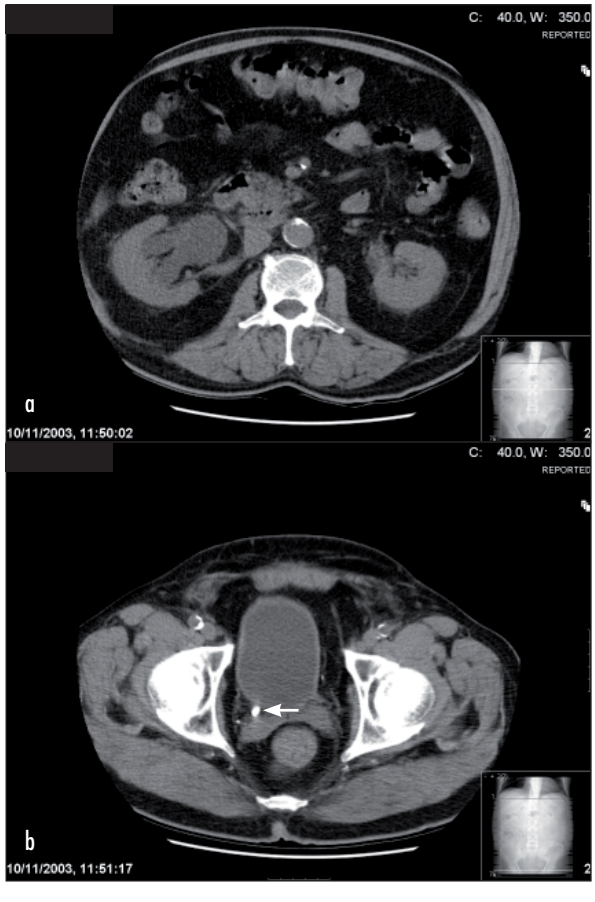
avoid renal failure and lactic acidosis. Metformin may only be resumed after confirmation of normal serum creatinine levels (Thomsen and Morcos, 2003).

Computed tomography

CT is more sensitive than IVU or ultrasound in detecting small renal lesions. A contrast-enhanced CT scan can determine whether cystic renal lesions are malignant by examining the change in Hounsfield units on enhancement (Benjaminov et al, 2006). The other advantage of CT is its ability to detect urinary tract calculi. Over 99% of stones, including those that are radiolucent on plain abdominal radiograph (uric acid and xanthine stones), will be seen on non-contrast helical CT (*Figure 1*). Pure matrix stones and stones made of indinavir are the exceptions. Non-contrast helical CT has now overtaken the IVU as the investigation of choice for diagnosing urinary tract calculi.

Traditionally CT has had a higher radiation dose compared to IVU, which discouraged its greater use. However, modern CT protocols can achieve radiation doses that approach the dose of the IVU (Dalla Palma et al, 2001).

Figure 1. a. Non-contrast helical computed tomography scan of a patient presenting with haematuria and right-sided loin pain. The right kidney is dilated with perinephric stranding and thickening of the Gerota's fascia. b. Image from the same patient, showing that the cause of the right-sided hydronephrosis is a stone (arrowed) at the vesico-ureteric junction.



Apart from the radiation burden and cost, disadvantages of CT include its limited availability, especially in an acute setting, and the need for specialists to interpret the images. Currently the role of CT urography is being investigated, and it is predicted that with the necessary technical improvements this technique will replace the IVU for detecting urothelial lesions in the upper urinary tract (Korobkin, 2005). If so, CT may become the only imaging investigation needed in the assessment of the upper urinary tract in haematuria.

Magnetic resonance imaging

The detection rate of renal masses on MRI is comparable to CT. The slightly poorer resolution of the urinary tract on MRI compared to CT has meant that CT is more widely used compared to MRI. However, MRI has certain advantages over CT. Magnetic resonance urography does not require potentially nephrotoxic contrast media and therefore can be used in patients irrespective of renal function. Similar to CT, it can also combine angiography and urography in the same examination. It may be used in patients in whom other investigations are contraindicated, for example pregnant woman. Although maximum intensity projection reconstructions from three-dimensional datasets can resemble a conventional IVU, as yet the spatial resolution is inferior to alternative techniques. Disadvantages of MRI include its high capital cost and limited availability. Patients with claustrophobia or metal implants are not suitable for scanning. The advantages and disadvantages of the different imaging methods are summarized in *Table 1*.

Angiography

Arteriography has now been superseded in the investigation of haematuria by CT or MR angiography. The primary role for angiography is currently for treating acute renal haemorrhage during embolization.

Virtual endoscopy

Volume-rendered three-dimensional reconstruction of CT and MRI data can be explored with the technique of perspective rendering in which the computer simulates an endoscopic view of a hollow viscus or body cavity – so-called 'virtual endoscopy'. Virtual endoscopy has inherent advantages in that it is non-invasive and therefore avoids the risk of perforation, stricture formation or infection. The role of virtual upper tract endoscopy (ureterorenoscopy) and cystoscopy in the evaluation of the urinary tract is still being defined, but it is likely that it will be useful in evaluating patients where endoscopy is difficult either as a result of anatomy or disease (e.g. strictures) (Ghani et al, 2004).

Endoscopy

The main purpose of endoscopy is to exclude tumour within the urinary tract. It is ideal if results of upper tract imaging are available before lower tract endoscopy is

undertaken so that any equivocal or abnormal result can be evaluated further during endoscopy.

Cystoscopy (lower tract endoscopy)

Flexible endoscopy

The diagnostic accuracy of flexible cystoscopy is equivalent to rigid cystoscopy if the urine is clear. For lesions at the bladder neck, it may be superior to rigid cystoscopy (Grossfeld et al, 2001). Flexible cystoscopy is the investigation of choice as it is well tolerated under local anaesthesia, and has less pain and fewer complications than rigid cystoscopy. It can be performed quickly in an office setting allowing rapid evaluation of the lower tract. Flexible cystoscopy also enables treatment of small transitional cell carcinomas with laser or cystodiathermy.

Rigid endoscopy

The indications for rigid cystoscopy include persistent gross haematuria, diagnostic uncertainty at flexible cystoscopy and where access to the bladder is restricted as a result of disease (urethral stricture, large prostate).

Retrograde ureteropyelography

Retrograde ureteropyelography at the time of cystoscopy can confirm the presence of a known or suspected filling defect on IVU or discover further abnormalities.

Upper tract urine cytology

Voided urine cytology has poor sensitivity for low/moderate grade upper tract transitional cell carcinoma unless the lesion is carcinoma in situ or high grade. The diagnostic yield of cytology can be significantly increased if selective upper tract urine cytology is performed on urine obtained using a ureteric catheter. Retrograde brushings can also increase the sensitivity and specificity of cytological analysis.

Ureterorenoscopy

Evidence of an upper tract abnormality on imaging may warrant further evaluation with upper tract endoscopy. Diagnostic ureterorenoscopy is then indicated in suspected upper tract transitional cell carcinoma, for biopsy confirmation and cellular staging. Frank haematuria that is unilateral and supravesical in origin, and which cannot be diagnosed by routine radiological, cytological or haematological investigations, is known as benign lateralizing haematuria. Benign lateralizing haematuria is an indication for upper tract endoscopy, and its management is described later on.

Renal biopsy

Microscopic haematuria in the presence of proteinuria (>500 mg of protein in the urine/24-hour collection), red blood cell casts, dysmorphic red blood cells or an elevated serum creatinine level should be evaluated by a nephrologist for renal parenchymal disease. The limit of detection of standard urine dipsticks for proteinuria is 300 mg/litre. Haematuria of urological origin does not elevate protein concentration greater than 200–300 mg/dl (+2 to +3 on disptick).

Table 1. Advantages and disadvantages of the main imaging modalities used to investigate haematuria

	Advantages	Disadvantages
Ultrasound	Non-ionizing, portable, less expensive, good for detecting mass lesions >3 cm and hydronephrosis, no preparation required	Operator dependent, poor at detecting ureteric and small renal (<5 mm) calculi, imaging suboptimal in obese patients
Intravenous urography	Excellent for detecting urothelial lesions, suitable for diagnosing calculi, easy to obtain	Poor for detecting small renal masses, potentially nephrotoxic, risk of adverse reaction from contrast agents, patient preparation required, considerable radiation exposure
Computed tomography	Unsurpassed for diagnosing calculi, excellent for detecting mass lesions	Significant radiation exposure, risk of adverse reaction from contrast (if used), expensive; may not visualize bladder clearly if there are prosthetic hip joints
Magnetic resonance imaging	Can be used in pregnancy, no risk of contrast reaction, suitable in renal failure	Limited availability, may induce claustrophobia, unsuitable for patients with metal implants/pacemakers (unless using open magnet magnetic resonance imaging)

Management

Delaying immediate investigation

Referral to a urologist may be delayed in the following situations:

- Haematuria in the presence of a positive urine culture – although men should be investigated after a single episode, women should be treated with culture-specific antibiotics. Persistent haematuria after treatment with no evidence of infection warrants investigation. Microscopic haematuria in women who have repeated urinary tract infections should also be investigated
- Exercise haematuria – persistent haematuria after 48–72 hours of rest requires investigation
- Menstruation-associated haematuria – haematuria during menses should be confirmed with a mid-cycle urine analysis before investigation.

Asymptomatic microscopic haematuria

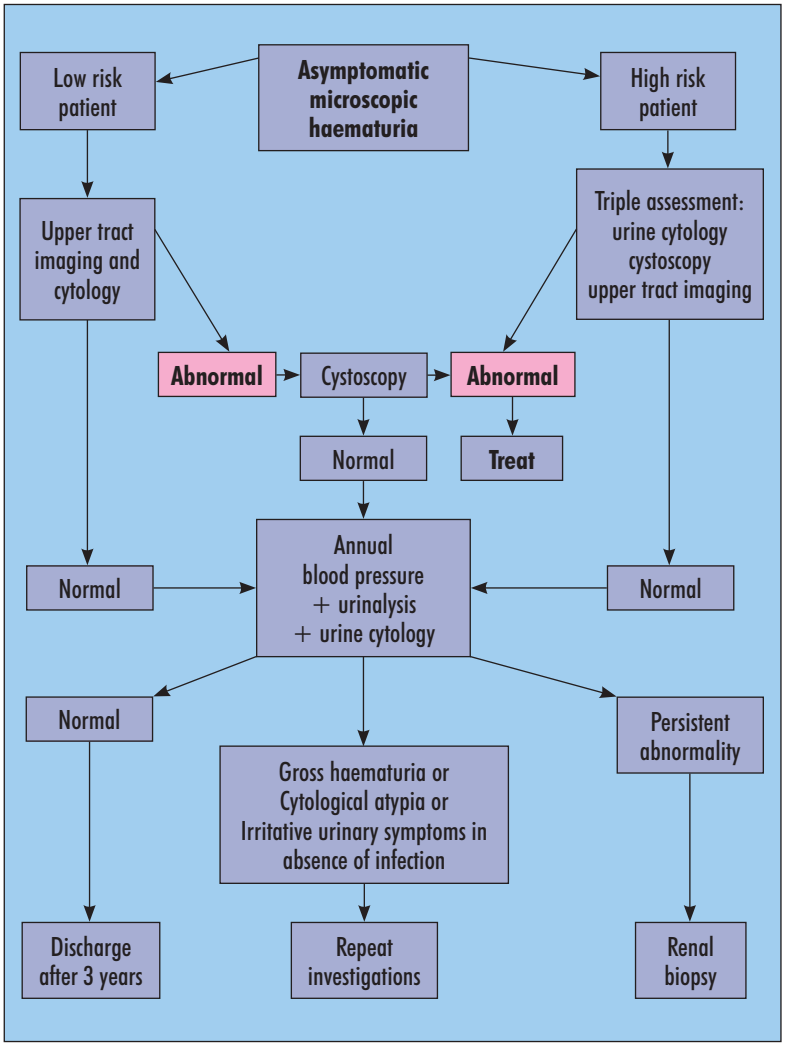
Urological cancer may be present in 0.5–8.3% of patients with asymptomatic microscopic haematuria (Tomson and Porter, 2002). The risk of cancer increases with age and where there is a history of exposure to carcinogens.

The American Urological Association policy committee have divided patients with asymptomatic microscopic haematuria into high and low risk groups (Grossfeld et al, 2001). Patient risk factors for developing urological cancer were detailed in the first of these two

articles. A single episode of microscopic haematuria (regardless of the method of analysis) in a patient with any of these risk factors should lead to thorough first-line evaluation consisting of urine cytology, upper tract imaging and lower tract endoscopy. Patients with asymptomatic microscopic haematuria and a low risk of malignancy do not necessarily require all of these investigations. In these patients, imaging of the upper tract is the primary investigation followed by cystoscopy if imaging is abnormal. If upper tract imaging is normal, urine cytology should be evaluated, followed by cystoscopy if cytology is abnormal or atypical (*Figure 2*).

For upper tract imaging, the choice remains between IVU, ultrasound and CT. An ultrasound and plain abdominal radiograph may be sufficient in low risk patients. High-risk patients should ideally undergo IVU and ultrasound, as there is a risk, albeit small, of missing cancer if only one of these modalities is used (Khadra et al, 2000). High-risk patients allergic to contrast medium are recommended to undergo retrograde ureteropyelography instead of IVU.

Figure 2. Management of asymptomatic microscopic haematuria (based on American Urological Association guidelines; Grossfeld et al, 2001).



Gross haematuria

The consequences of significant gross haematuria are occasional haemodynamic compromise and clot retention. Patients who are haemodynamically unstable or in urinary retention require emergency admission to hospital and volume resuscitation. They may require blood transfusion and close monitoring. Clot retention is treated by inserting a large bore three-way urethral catheter. Liberal bladder washouts should be performed until all clots have been evacuated. If the urine remains bloody, continuous irrigation of the bladder with saline through the third port of the catheter is started to avoid clot formation and further retention. An accurate account of fluid input and output should be recorded. The rate of irrigation is reduced when the urine becomes less blood stained.

This conservative approach is sufficient in managing the acute consequences of gross haematuria in the vast majority of patients. Upper tract imaging and urine cytology may be carried out in the interim period while the haematuria is resolving. If the urine becomes clear, flexible cystoscopy can be carried out under local anaesthesia to assess the lower tract. Rigid cystoscopy under general anaesthesia should be done where bleeding has not ceased. In theatre, bleeding can be controlled by evacuation of clots and coagulation of bleeding points. Biopsies may be taken to obtain a diagnosis.

Benign lateralizing haematuria

Benign lateralizing haematuria is a diagnostic and therapeutic challenge. As first- and second-line investigations fail to identify a suitable cause for the bleeding, ureterorenoscopy assumes a pivotal role in diagnosis and therapy. Ureterorenoscopy usually identifies the bleeding to be emanating from a vascular lesion in the kidney, and through a combination of direct vision and biopsy, malignant lesions are ruled out. Endoscopic treatment is the mainstay of the management for benign lateralizing haematuria. Up to half of patients undergoing ureterorenoscopy will have a discrete vascular lesion that can be treated. Diathermy fulguration and laser ablation are two effective treatments, with a higher success rate for discrete lesions than for diffuse lesions (Rowbotham and Anson, 2001).

Intractable haematuria

Severe haematuria may occur as a result of radiation cystitis, bladder carcinoma, cyclophosphamide-induced cystitis and severe infection. Very rarely, fulguration of the bleeding lesion and subsequent irrigation on the ward through a three-way urethral catheter fails to stop bleeding. Such patients with massive uncontrollable haematuria will require other measures to stop bleeding. These include alum irrigation, hydrodistension, formalin instillation, hyperbaric oxygen treatment, radiotherapy and embolization. Some of these methods have significant morbidity and urological sequelae and are only used when life is at risk and/or the patient is unable to tolerate a cystectomy (Choong et al, 2000).

Follow up of patients with negative investigations

Urological

The concern with haematuria is that malignancy may be missed. Data from studies following up patients with normal initial evaluation have demonstrated that the prevalence of malignancy is more or less non-existent. In one study of 191 patients followed up for 20 years with urine analysis, cytology, biennial cystoscopy and IVU, malignancy was not detected (Howard and Golin, 1991). In a large study by Khadra et al (2000), subsequent follow up (range 2.5–4.2 years) of patients with no abnormal findings revealed no cancers. This evidence provides reassurance to specialists who are able to discharge patients back to the GP who should repeat urinalysis and urine cytology on an annual basis. A full evaluation including imaging and cystoscopy should occur if the cytology is abnormal or symptoms develop.

Nephrological

The role of renal biopsy in patients with isolated haematuria has not been defined. Although many such patients may have structural glomerular abnormalities, they appear to have a low risk for progressive renal disease. The natural history of patients diagnosed with immunoglobulin A nephropathy and isolated microscopic haematuria is usually benign. In up to half, haematuria will disappear, 20% will have intermittent haematuria and in the remainder haematuria will persist. Some of these patients may develop hypertension and proteinuria over 5–10 years. The presence of proteinuria is the single biggest risk factor for progression of renal disease. Without proteinuria the risk of renal impairment is low and that of end-stage renal failure is extremely low. In the presence of significant proteinuria, hypertension, elevated serum creatinine and additional abnormalities on renal biopsy, the risk of end-stage renal failure at 20 years may be as high as 30% (Tomson and Porter, 2002).

Follow up of persistent haematuria, either in the presence of a normal previous renal biopsy or where biopsy was not performed, should be with yearly evaluation by the GP to exclude the development of hypertension, proteinuria or renal insufficiency.

Conclusions

The primary aim of imaging is to determine the cause of bleeding. First-line imaging investigations commonly include ultrasound and plain abdominal X-ray of the urinary tract. CT is the standard for defining renal tumours while IVU is better at diagnosing upper tract urothelial tumours. In the future, the CT urogram may become the single definitive imaging investigation. Endoscopy helps to visually confirm the source of bleeding whether it is from the upper or lower urinary tract. Lesions can be biopsied or excised completely using electrocautery or laser coagulation. Patients with no source of bleeding identified after undergoing all investigations are kept under yearly primary care surveillance with assessment of urine cytology, serum creatinine, blood pressure and proteinuria. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Using only one imaging investigation for haematuria misses pathology.
- High risk haematuria should have triple assessment with urine cytology, cystoscopy and upper tract imaging.
- Non-contrast computed tomography is the gold standard investigation for diagnosing urinary tract calculi.
- Haematuria of urological origin does not elevate protein concentration to more than +2 to +3 on a dipstick.
- Proteinuria is the single biggest risk factor for progression of renal disease in glomerular bleeding.