Chapter 20 An Approach to Haematuria and Proteinuria

Clinical Case

A 30-year-old nurse is referred for haematuria. She has had intermittent episodes of haematuria for the last 1 to 2 years, with no other symptoms. In particular, she has no dysuria, loin pain, fever, joint pains or rash. On examination, her blood pressure is 152/94 mmHg. The examination is otherwise normal, with no skin or joint abnormalities. Blood tests reveal a creatinine of 123 umol/L, with normal full blood count, electrolytes and liver function. Urine investigations show 35 red cells (75% dysmorphic) and three white cells per high powered field, with no casts, and a urine protein creatinine ratio of 0.2 g/mmol. What is the most likely diagnosis, and what further investigations would you perform?

Macroscopic haematuria presents as visible red or brown urine. **Microscopic haematuria** is detectable only on urine examination; urine is not discoloured but microscopy reveals ≥ 3 red blood cells (RBC) per high power field. **Proteinuria** is the presence of urinary protein above physiological limits, which may present as frothy urine, frank nephrotic syndrome, or be asymptomatic and detected on urine dipstick.

Clinical Syndromes

It is clinically helpful to first identify the clinical picture:

a. **Isolated haematuria:** Without proteinuria, oedema, hypertension or renal insufficiency.

b. **Nephritic syndrome:** Haematuria ± pyuria ± casts, with hypertension and impaired renal function (raised creatinine). There may be varying degrees of proteinuria and oedema.

c. **Rapidly progressive glomerulonephritis** (RPGN, crescentic glomerulonephritis [GN]): Acute-onset nephritic features quickly leading to acute kidney injury (AKI) and oliguria over a short duration (days–months). This corresponds to a histological picture of crescent formation on renal biopsy.

d. **Isolated proteinuria:** Proteinuria less than nephrotic range (< 3 g/day), without haematuria, oedema, hypertension or renal insufficiency.

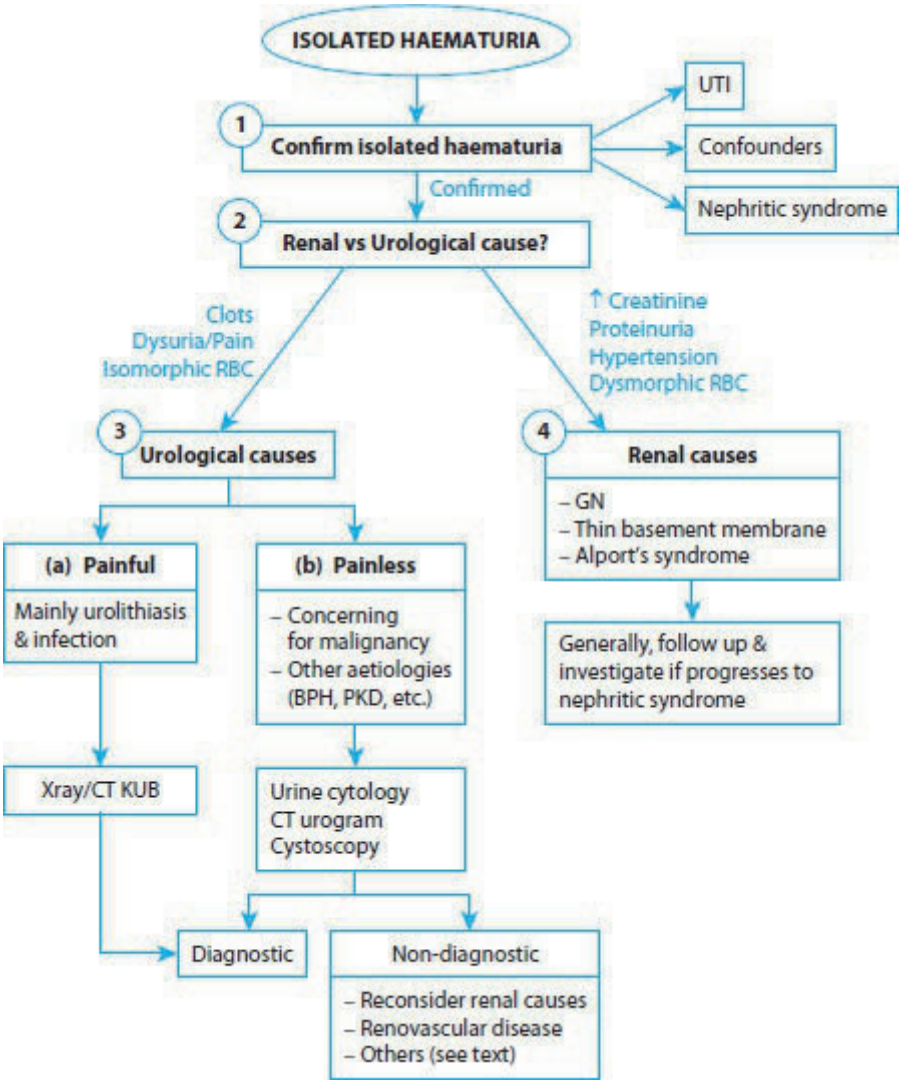
e. **Nephrotic syndrome:** Nephrotic-range proteinuria (> 3 g/day), hypoalbuminaemia, oedema, ± hyperlipidaemia, with minimal haematuria and urinary casts.

f. **Chronic kidney disease** (CKD): The end stage of renal damage, which not uncommonly is the first presentation of renal disease (see Chapter 18).

Each syndrome is discussed in turn, considering both renal and urological aetiologies. Yet these syndromes are closely related and cannot always be clearly distinguished. At times the clinical picture is an overlap (e.g., a mixed nephritic–nephrotic pattern). Other times the syndromes are a spectrum—for instance, a GN may begin as isolated haematuria, progress through nephritic syndrome, and end as CKD. Finally, one aetiology (esp. lupus nephritis) may present with different syndromes. CKD is the common end-stage for untreated progressive GN.

A. Isolated Haematuria

The approach to isolated haematuria is given (Figure 20.1).



BPH, benign prostatic hyperplasia; GN, glomerulonephritis; PKD, polycystic kidney disease; UTI, urinary tract infection.

Figure 20.1. Approach to isolated haematuria.

1. Confirm Isolated Haematuria

Ensure that the clinical picture is an otherwise well patient with nothing more than isolated haematuria. In particular:

(a) **Rule out urinary tract infection (UTI):** Acute onset dysuria, frequency or cloudy urine suggests infection (Chapter 21). Look at the dipstick for nitrite and leukocyte esterase, and urine full examination microscopy (UFEME) for pyuria.[1]

(b) **Exclude confounders:** Haematuria in an asymptomatic patient may not be true haematuria.

- **Menstrual blood contamination:** Repeat a sample after menstruation ceases; consider menarche or post-menopausal bleed in non-reproductive age groups.
- **Benign trauma:** For example, preceding sports, sex, recent cystoscopy, traumatic catheterisation. Repeat the sample.
- **Obstructive jaundice:** 'Tea-coloured' urine mimics haematuria; look for scleral icterus, biliary symptoms (Chapter 10).

Where urine is red but UFEME shows no RBCs, centrifuge the urine. In true haematuria, RBCs settle into a red sediment, and the supernatant remains clear. A red supernatant is not haematuria, and should be tested for heme with a dipstick. Interpretation:

- **Supernatant clear, sediment red:** True haematuria.
- **Supernatant red, dipstick heme positive:** Haemoglobinuria (e.g., haemolysis, see Chapter 32), myoglobinuria (rhabdomyolysis).
- **Supernatant red, dipstick heme negative:** Porphyria, red beets, drugs (e.g., rifampicin, phenolphthalein, phenytoin, quinine).

(c) **Nephritic syndrome:** If there is grossly elevated creatinine, hypertension and peripheral oedema, approach as for nephritic syndrome (page 194).

2. Consider If Renal vs. Urological

At times, either a renal or urological aetiology is apparent, other times, both workups may have to proceed in parallel. Certain clinical features favour one but are not absolute:

- **Urine:** Clots or bright red gross haematuria favour urological disease; microscopic haematuria may be of either urological or renal origin. Frothy urine suggests proteinuria and hence renal disease.
- **Urinary symptoms:** Lower urinary symptoms (e.g., dysuria, frequency, hesitancy, dribbling) suggest urological causes. On the other hand, their absence does not rule out urological disease.

- **Systemic features:** Hypertension, raised creatinine, oliguria, fluid overload, prominent lethargy and a known autoimmune disease favours renal differentials.

Urinalysis provides further clues:

- **UTI:** Should be ruled out in all patients.
- **Proteinuria:** Suggests a renal cause.
- **Casts:** These cylindrical structures take the shape of the renal tubular lumen in which they form, and are reasonably specific for renal disease.
  - **Muddy brown granular casts:** Acute tubular necrosis (ATN).
  - **Tubular epithelial cell casts:** Desquamation of tubular epithelium, for example, proliferative GN, ATN, acute interstitial nephritis (AIN).
  - **RBC casts:** Glomerular damage, for example, GN.
  - **WBC casts:** Inflammatory (e.g., proliferative GN, AIN) vs. infective (pyelonephritis).
- **Crystalluria:** Urate nephropathy.
- **Phase contrast microscopy:** This exploits the observation that passage through glomeruli and tubules may deform RBCs. Hence, > 80% dysmorphic RBC is likely of glomerular origin, implying a renal disease. > 80% isomorphic RBC is more likely non-glomerular. This test depends on the availability of skilled lab personnel; 20% to 80% dysmorphic is a grey zone.

3. Urological Aetiologies and Workup

Divide the urological aetiologies into those with loin pain, and those without.

(a) Painful Haematuria

The main considerations are:

- **Urolithiasis:** Episodes of loin-to-groin colic are classic (page 94).
- **Infection:** There will also be flank pain, fever and potentially systemic toxicity. Rule out complications, for example, pyonephrosis,

emphysematous pyelonephritis (Chapter 21).

- **Recent instrumentation** including catheterisation can cause traumatic haematuria.

Workup:

- Imaging may begin with a kidneys–ureter–bladder (KUB) X-ray or CT KUB. These non-contrast studies are appropriate in a history typical for stone disease with low suspicion of cancer; consider CT urogram instead if there is concern of malignancy.
- Recurrent stone formers may benefit from an evaluation to identify aetiologies of stone formation. Consider lifestyle factors (fluid intake), systemic disease (e.g., gout and hyperparathyroidism), 24 hr urine collection and metabolic workup (pH, Ca^{2+}, Mg^{2+}, citrate, oxalate, PO_4^{3-}, uric acid, cysteine) with paired serum electrolytes.

(b) Painless Haematuria

The timing of haematuria may be valuable: Initial haematuria suggests a urethral origin, terminal haematuria indicates bladder outlet, neck or prostatic urethra and haematuria occurring throughout micturition suggest upper urinary tract or upper bladder. Aetiologies include:

- **Malignancy**, including renal cell, urothelial and bladder cancers. This is the main concern in painless haematuria, and suspicion increases with age. Look for risk factors (e.g., smoking, occupational chemical exposure, pelvic radiation, schistosomiasis), and constitutional symptoms.
- Causes of painful haematuria (e.g., urolithiasis) may present atypically without pain; these will be revealed on imaging.
- **Benign prostatic hyperplasia (BPH):** Haematuria is an atypical presentation, lower urinary tract symptoms being more common. See Chapter 21.
- **Papillary necrosis:** In patients with chronic analgesia use, diabetes or ischaemic risk factors (e.g., vasculitis).
- **Polycystic kidney disease:** A patient with known polycystic kidneys, presenting with haematuria, may have bled into his cyst.

Workup: The aim of workup is to rule out malignancy. Perform:

- **Urine:** Cytology, as well as UFEME and culture if not already done.
- **Imaging:** CT urogram is ideal. This is a triphasic contrast CT (plain, parenchymal and excretory phases) which allows identification of stones, masses, filling defects and urinary system dilation proximal to an obstruction.
- **Cystoscopy:** This directly visualises and biopsies bladder tumours, it is necessary as imaging is less sensitive for bladder cancers, and should be done even if CT urogram finds an upper tract tumour (there is a 50% risk of synchronous bladder tumour).

Further workup—consider if the above are negative:

- Reconsider glomerular causes, for example, IgA nephropathy (see the following).
- Hypercalciuria, hyperuricosuria: May predispose to formation of small calculi.
- Renovascular diseases: For example, renal artery embolism, renal vein thrombosis, nutcracker syndrome, AV malformation.
- Bleeding diathesis: But do not ascribe haematuria simply to coagulopathy, without excluding sinister causes.
- Follow up for resolution of haematuria, especially in older patients at higher risk of malignancy.

4. Renal Aetiologies

These aetiologies may present with isolated haematuria and no other worrisome features (proteinuria, raised creatinine, hypertension).

- **Mild glomerulonephritis**, for example, IgA nephropathy (see Section ‘Nephritic Syndrome’).
- **Thin basement membrane disease (familial benign haematuria):** Intermittent episodes of haematuria with a positive family history of haematuria without renal failure. This is a benign disease.
- **Alport’s syndrome:** A genetic syndrome of haematuria, bilateral

sensorineural hearing loss ± ocular changes. There may be a positive family history.

The majority of patients with asymptomatic isolated haematuria and normal renal function (and who have been urologically cleared) do not develop progressive renal disease. Autoantibodies may be performed (see Section 'Nephritic Syndrome'), but renal biopsy is usually deferred and performed only if there is progression to frank nephritic syndrome.

B. Nephritic Syndrome

In the nephritic syndrome, inflammatory glomerular damage makes itself known with haematuria ± pyuria ± casts, and mild-moderate proteinuria. As glomerular damage progresses, glomerular filtration rate (GFR) falls and creatinine rises; hypertension and mild-moderate oedema develops. Clinical features and serological results may suggest a diagnosis; renal biopsy is usually performed in most patients.

Aetiologies and Clinical Features

(a) **Known history of infection**

- **IgA nephropathy** (synpharyngitic haematuria): This is the most common cause of nephritic syndrome. Clinically, it presents as one or several episodes of haematuria, each < 5 days after a viral respiratory illness. Haematuria may persist between episodes. Progressive proteinuria and renal insufficiency can develop over time, especially if the patient already has proteinuria or raised creatinine.

Workup

– Normal complement levels
– No serology available, no role for IgA levels

Henoch–Schonlein purpura is a closely related IgA deposition disease, which develops in children and teenagers, classically with a purpuric rash on lower limb extensors, arthralgia, abdominal pain ± nephritic syndrome.

- **Infection-associated GN:** This used to be called *post-infectious* GN, where skin or throat infection with a nephritogenic *Streptococcus pyogenes* strain results in haematuria 1 to 3 weeks later. Recently, it was recognised that GN can occur concomitantly with staphylococcal and streptococcal infection. Prognosis is good, typically with complete resolution of haematuria.

  – Evidence of streptococcal infection, for example, anti-streptolysin O titre
  – Complement levels: low C3 with normal C4

- **Subacute endocarditis:** Medical students memorise that this may cause immune complex phenomena including Osler nodes and haematuria. Keep in mind especially if blood cultures are positive for typical organisms that cause endocarditis, or there are risk factors (e.g., IV drug use, prosthetic valves).

  – Blood cultures
  – Echocardiogram

(b) **Multiorgan involvement** suggests a rheumatologic disease, for example,

- **Lupus nephritis:** There may be other manifestations involving the skin (alopecia, malar rash, ulcers), serosa (pleuritis, pericarditis), joints (arthritis), bone marrow (cytopenias), nerves and other

  – Antibodies: ANA, dsDNA, ENA (anti-Sm, anti-Ro anti-La)
  – Complement consumption: low C3, C4

organs.

- **Antineutrophil cytoplasmic antibody (ANCA) vasculitis:**
  - **Granulomatosis with polyangiitis** (Wegener's granulomatosis): Causes fever, otolaryngological (otitis media, hearing loss, nasal discharge, ulcers), lung (cough, dyspnoea, haemoptysis, CXR nodules and infiltrates), nerve (mononeuritis multiplex), joint (polyarthritis) and skin (purpura) involvement.
  - **Microscopic polyangiitis:** As for Wegener's, but with less profound otolaryngological or lung disease.
  - **Eosinophilic granulomatosis with polyangiitis** (Churg–Strauss syndrome): Asthma, eosinophilia, otolaryngological disease (allergic rhinitis, nasal polyposis, otitis media with effusion, etc.), tender subcutaneous granulomas, heart disease (failure, arrhythmia, pericarditis); also involves nerves (mononeuritis multiplex), gut and other organs.

  – ANCA
  – Test for other organ involvement, for example, liver function

- **Anti-GBM disease (Goodpasture's syndrome):** Glomerulonephritis and alveolar haemorrhage (haemoptysis, infiltrates on CXR).

  – anti-GBM antibody

(c) **No symptoms other than nephritic syndrome itself:** Most commonly IgA nephropathy, also consider lupus nephritis (renal disease may precede or

– Antibodies above

be separate from other manifestations). Serology and biopsy would be necessary for diagnosis.

Workup

In practice, the following workup is standard:

- All of the earlier antibodies are sent.
- Screening tests for hepatitis B, C and HIV (these can present with glomerulonephritis, but positive serology does not prove that glomerulonephritis is due to these viruses).
- Ultrasound of the kidneys.

Renal biopsy is performed in most patients to establish the diagnosis, determine prognosis (activity, scarring) and guide therapy. One exception is a clear-cut infection-associated nephritis, in which prompt recovery of glomerulonephritis would be expected. Biopsy may reveal:

- **Immune complex deposition:** Granular staining pattern as glomeruli are marked by deposited immune complexes for autoimmune attack. Specific immunoglobulin/complement types are deposited in each disease, for example, IgA in IgA nephropathy, ‘full house’ pattern in lupus.
- **Linear staining** of glomerular capillary walls is found in anti-GBM disease.
- **Pauci-immune pattern:** No immunofluorescence on biopsy—classically in ANCA vasculitis.

C. Rapidly Progressive GN

This is essentially an extreme presentation of nephritic syndrome; aetiologies are that of nephritic syndrome. On the other hand, aetiologies of nephrotic syndrome tend not to present this dramatically. Some notes:

- A biopsy is necessary. This will show crescents and identify the aetiology.
- In the presence of lung haemorrhage, consider the pulmonary–renal

syndromes including ANCA vasculitis, anti-GBM disease and lupus.

D. Isolated Proteinuria

Proteinuria may be detected in a number of ways. The gold standard, 24-hr urine protein, is very inconvenient. The spot protein–creatinine ratio is a more convenient test, but may be unreliable in AKI, or in a very muscular or cachectic patient (Table 20.1).

Table 20.1. Detection of Proteinuria

	24 hr urine[a]	Protein/creatinine ratio (PCR)[b]
Microalbuminuria	30–300 mg/day	> 2.5 (male), > 3.5 (female) mg/mmol
Proteinuria	> 0.3 g/day	> 30 mg/mmol
Nephrotic range	> 3 g/day	> 300 mg/mmol

[a]For a 1.73 m^2 person; adjust value for children or very large/small. Microalbuminaemia is only of value in diabetic nephropathy.

[b]To convert PCR from mg/mmol to mg/g, multiple values by 10.

In asymptomatic patients with isolated proteinuria, the focus is to verify sustained proteinuria, and consider secondary causes. Patients with concomitant haematuria, nephrotic-range proteinuria, renal insufficiency or oedema should be considered for primary glomerular disease.

1. Verify Sustained Proteinuria

- Ensure that the patient is not having a UTI: This may cause falsely elevated protein.
- **Do not use dipstick alone:** Patients are commonly referred for proteinuria after positive dipstick testing. This is less reliable; false positives are seen with iodinated contrast, haematuria and pyuria. On the other hand, microalbuminaemia and non-albumin proteinuria (e.g., myeloma) are missed on dipstick.

- **Repeat urinary protein screening.** Transient proteinuria is common (e.g., due to exercise, fever, stress). A single result showing proteinuria of < 1 g/24 hr, with a negative repeat screen, is of no clinical significance.
- **Test first urine sample after overnight rest:** Orthostatic proteinuria is a phenomenon of increased protein excretion when upright but normal when supine, and is also clinically unimportant.

2. Consider Secondary Causes of Proteinuria

- **Diabetic nephropathy:** Microvascular damage from sustained hyperglycaemia occurs in diabetes. Nephropathy begins as microalbuminaemia, progresses into proteinuria, and CKD sets in over many years. Diabetic nephropathy is usually diagnosed presumptively, but other aetiologies should be considered (and biopsy pursued) if GFR declines rapidly, if there is an active urinary sediment with haematuria and casts, or if there are signs and symptoms of a multi-system disease (e.g., suspect autoimmune disease).
- **Myeloma cast nephropathy:** The excreted protein in myeloma is actually immunoglobulin light chains. Suspect the diagnosis in older patients with features of hyper**c**alcaemia, ***r***enal impairment, ***a***naemia and ***b***one pain (the 'CRAB' features). If suspicious, do a myeloma screen (serum and urine protein electrophoresis, plus serum free light chains).
- **Amyloidosis:** Primary in underlying plasma cell disorders (e.g., myeloma), or secondary to chronic inflammatory states (e.g., rheumatoid arthritis and ankylosing spondylitis). There may be multi-organ involvement and this is usually confirmed on biopsy (usually of abdominal fat pad or rectum, rather than kidney).
- **Hypertension:** Uncontrolled hypertension causes hypertensive nephrosclerosis. In the setting of renal failure or other target organ damage (chest pain, pulmonary oedema, aortic dissection, papilloedema, etc.), this is treated as a hypertensive emergency. In the pregnant lady, consider pre-eclampsia.
- **Structural renal causes:** For example, reflux nephropathy, polycystic kidney disease.

3. Consider Primary Glomerular Disease

Almost all causes of nephrotic syndrome can present with sub-nephrotic proteinuria. Consider a basic autoimmune screen (ANA, ANCA) and hepatitis serologies. Discuss renal biopsy should proteinuria become nephrotic, or should haematuria or renal insufficiency develop on subsequent follow up.

E. Nephrotic Syndrome

In the nephrotic syndrome, there is increased filtration of macromolecules and heavy proteinuria (> 3 g/day), leading to hypoalbuminaemia and therefore oedema. There is minimal haematuria. Creatinine is normal or only slightly elevated at first presentation, but with persistent hyperfiltration, renal function declines over months to years.

Adults with nephrotic syndrome should receive (1) renal biopsy, (2) serology to look for secondary causes and (3) workup for complications of nephrotic syndrome. Some patients with diabetic nephropathy progress into nephrotic-range proteinuria over many years; biopsy is often omitted if there is a clear long-standing history of poorly controlled diabetes, and there are no atypical features leading to suspicion of other differentials.

1. Biopsy

Biopsy may reveal the following entities. They generally have little intra-glomerular immune complex deposition, and therefore little inflammation and haematuria. These are histological pictures and not in themselves diseases; each histological picture may be primary (idiopathic) or secondary to another disease.

- **Minimal-change disease** (nil lesion): The majority are idiopathic.
- **Focal segmental glomerulosclerosis** (FSGS): May be primary or secondary; secondary causes include drugs, infection and any entity that decreases nephron mass.

- **Membranous glomerulonephritis** (MGN): Primary vs. secondary due to lupus, malignancy, drugs, hepatitis B and C. 70% to 80% of primary MGN are positive for anti-phospholipase A2 receptor (anti-PLA2R) antibodies, while secondary MGN is rarely positive; therefore, positive anti-PLA2R suggests primary MGN, negative anti-PLA2R may be either primary or secondary MGN and workup for secondary causes would be indicated.
- **Membranoproliferative glomerulonephritis** (MPGN): Classify based on immunofluorescence findings into:
  - Immune complex mediated: Due to infections, autoimmune disease and monoclonal gammopathy of unknown significance (MGUS).
  - Complement mediated, due to dense deposit disease or C3 glomerulonephritis.
  - Neither: For example, healing thrombotic thrombocytopenic purpura.
- **Lupus nephritis** (Class V).

2. Consider Secondary Causes

The histological pictures may be secondary to other disease. Consider workup for:

- **Infection:** A non-exhaustive list includes HIV (FSGS), Hep B (MGN), Hep C (MPGN, MGN), parvovirus (FSGS), syphilis (MGN), malaria and schistosomiasis. As a minimum, do HIV and hepatitis serology.
- **Autoimmune:** Most often systemic lupus erythromatosis (SLE) (MPGN, MGN). Do lupus serology.
- **Malignancy:** MGN with negative anti-PLA2R is strongly associated with cancers, most commonly breast, lung and colon; this histological picture requires a malignancy workup. Minimal-change disease is associated with Hodgkin lymphoma.
- **Myeloma:** As discussed earlier.
- **Drugs:** For example, heroin, analgesics and pamidronate (FSGS); gold, penicillamine, NSAIDs, probenecid (MGN).
- **Diseases that decrease nephron mass:** May force remaining nephrons to hyperfiltrate, causing injury and FSGS. Aetiologies include—

hydronephrosis, hypertensive nephrosclerosis or anatomical abnormalities. It is important to identify this group of patients as they are usually not given immunosuppression. It may be apparent on past medical history; also obtain renal imaging (usually ultrasound kidneys and bladder).

3. Look for Complications

Protein loss in nephrotic syndrome may result in systemic complications that should be evaluated. This includes:

- **Severity of oedema:** May require management, e.g., diuresis.
- **Lipids:** Urinary loss of lipoproteins may lead to hyperlipidaemia.
- **Clotting risk:** Urinary loss of antithrombin may lead to hypercoagulability (PT/PTT may be normal but deep vein thrombosis [DVT]/pulmonary embolism [PE] risk is nonetheless increased).
- **Infection risk:** Due to immunoglobulin loss.

☞ Using what you have learnt, **pen down your approach** to the Clinical Case at the start of the chapter **BEFORE reading the discussion** below.

Case Discussion

This young lady has nephritic syndrome, evidence of which includes microscopic haematuria with renal insufficiency and hypertension (the phase contrast microscopy is technically not > 80% dysmorphic but it is suspiciously high). The history of intermittent haematuria suggests IgA nephropathy that is epidemiologically also the most common. If specifically asked, she may reveal a history of viral upper respiratory tract infection around each episode of haematuria. Lupus nephritis is the other aetiology to consider in a young lady; at present she has no suggestive systemic features, nonetheless it should be considered and definitively ruled out on biopsy and antibody testing. Elicit any history of haemoptysis, which would suggest anti-GBM disease.

Workup should include an anti-streptolysin titre (if currently having

haematuria), complement levels, autoantibodies (ANA, dsDNA, ENA profile, ANCA, anti-GBM antibody), hepatitis B and C as well as HIV screening. Renal biopsy should be pursued.

Key Lessons	1. Isolated haematuria may be due to renal or urological causes. Urological causes may be painful (e.g., urolithiasis) or painless (main concern is malignancy). Dysmorphic RBCs, proteinuria, renal insufficiency, hypertension and the presence of systemic autoimmune disease suggests a renal cause. 2. In patients with proteinuria, first exclude transient and orthostatic proteinuria. The causes of persistent proteinuria include diabetic nephropathy, myeloma and glomerular disease (especially in nephrotic-range proteinuria, or if there is haematuria or renal insufficiency). 3. Patients presenting with nephritic or nephrotic syndrome generally require renal biopsy. Each histological pattern may be secondary to a systemic cause, or a primary glomerular disease. Consider workup for infection (especially hepatitis, HIV), autoimmune disease (e.g., systemic lupus erythromatosis [SLE], ANCA vasculitis), malignancy and other causes as appropriate.
Common Pitfalls	1. Not all patients with haematuria should be referred to a urologist—first consider if haematuria might be of a renal aetiology! 2. Not every diabetic with chronic kidney disease has diabetic nephropathy—be alert for suspicious features, which suggest glomerulonephritis.
Questions	1. **REFLECT!** Have you ever encountered a patient with primary glomerulonephritis? How did the patient first present, and what did the investigations show? 2. **DISCUSS!** Many cases of haematuria or proteinuria can be managed by a non-specialist. What are the indications for urological or renal referral? 3. **EXPLORE!** Look up how a renal biopsy is performed. What are the complications and contraindications of this procedure? 4. **GO FURTHER!** Renal involvement is common in lupus. What are the different types of renal disease in lupus?

[1] Note that pyuria with negative urine cultures (sterile pyuria) may be seen in partially treated UTI, infection with fastidious organisms or tuberculosis (TB), prostatitis and other causes of urologic inflammation (urolithiasis, bladder tumour).

21

I have a patient with hematuria. How do I determine the cause?

Sachin Shah, MD

CHIEF COMPLAINT

PATIENT 

Mr. Y is a 56-year-old man who has had several episodes of red urine in the past few days.

What is the differential diagnosis of hematuria? How would you frame the differential?

CONSTRUCTING A DIFFERENTIAL DIAGNOSIS

Red urine is not always caused by hematuria. A variety of medications, food dyes, and metabolites can cause heme-negative red urine, or pigmenturia (Table 21-1). Furthermore, not all dipstick tests positive for blood are due to hematuria. In addition to detecting heme in intact red blood cells (RBCs), urine dipsticks detect free hemoglobin (commonly associated with hemolytic anemia) and myoglobin (commonly associated with rhabdomyolysis), hence leading to false-positive tests for hematuria.

Table 21-1. Causes of heme-negative red urine (pigmenturia).

Causes	Examples
Medications	Azathioprine Chloroquine Deferoxamine Doxorubicin Ibuprofen Iron sorbitol Laxatives Nitrofurantoin Phenazopyridine Phenytoin Riboflavin Rifampin
Food dyes	Beets Blackberries Food coloring
Metabolites	Bilirubin Melanin Methemoglobin Porphyrin Tyrosinosis Urates

Whenever the urine dipstick is positive for blood, and the microscopic exam of the urine does not show RBCs, myoglobinuria and hemoglobinuria should be considered.

True gross (visible) hematuria is always pathologic. Microscopic (nonvisible) hematuria may be transient, spurious, or persistent. Transient causes of microscopic hematuria include urinary tract infections (UTIs) (which sometimes also cause gross hematuria) and strenuous exercise; hematuria due to these causes would be expected to resolve on repeat testing after 48 hours of treatment or after discontinuing exercise for 72 hours. Spurious causes include urinary

contamination from menstruation and sexual intercourse in women. This chapter will focus on persistent, true hematuria.

All patients with hematuria should have a urine culture performed, regardless of the likelihood of infection.

The differential diagnosis of hematuria is often divided into microscopic hematuria or gross hematuria. Microscopic hematuria is present when microscopic inspection of at least 2 properly collected urine specimens show > 3 RBCs per high-powered field (hpf). Gross hematuria is red or brown urine, sometimes with blood clots. However, there is considerable overlap in the causes of microscopic and gross hematuria, and it may be more practical to first consider whether the hematuria is glomerular in origin. Pivotal points that help distinguish glomerular hematuria from nonglomerular hematuria include dysmorphic RBCs (acanthocytes), red cell casts, new or acutely worsening hypertension or proteinuria, and increased creatinine. While these abnormalities may also be seen in some of the interstitial and vascular causes of hematuria, they will not be found when hematuria is caused by a renal structural abnormality or an abnormality distal to the kidneys. Visible blood clots, which are never due to a glomerular cause, are another pivotal point, indicating a lower urinary tract source of the hematuria.

A. Renal

1. Glomerular

a. IgA nephropathy

b. Alport disease and thin basement membrane nephropathy (TBMN)

c. Other primary and secondary glomerulonephritides

(1) Postinfectious or infection-related

(2) Systemic lupus erythematosus

(3) Goodpasture syndrome

(4) Henoch-Schönlein purpura (HSP) and other small or medium vessel vasculitides

(5) Hemolytic uremic syndrome (HUS)

2. Nonglomerular

a. Neoplastic

(1) Renal cell or transitional cell carcinoma

(2) Benign renal mass

b. Tubulointerstitial

(1) Nephrolithiasis

(2) Polycystic kidney disease or medullary sponge kidney

(3) Pyelonephritis

(4) Acute interstitial nephritis

(5) Papillary necrosis

c. Vascular

(1) Arterial embolus or thrombosis

(2) Arteriovenous malformation or arteriovenous fistula

(3) Renal vein thrombosis

(4) Nutcracker syndrome (compression of left renal vein)

(5) Malignant hypertension

d. Metabolic (hypercalciuria, hyperuricosuria)

B. Extrarenal

1. Ureter

a. Mass: benign polyp or malignancy

b. Stone

c. Stricture

2. Bladder

a. Transitional cell or squamous cell carcinoma

b. Noninfectious cystitis (radiation or medication [cyclophosphamide])

c. Infectious cystitis

d. Stone

3. Urethra

a. Urethritis

b. Urethral diverticulum

c. Traumatic catheterization

d. Urethral stricture

5. Prostate

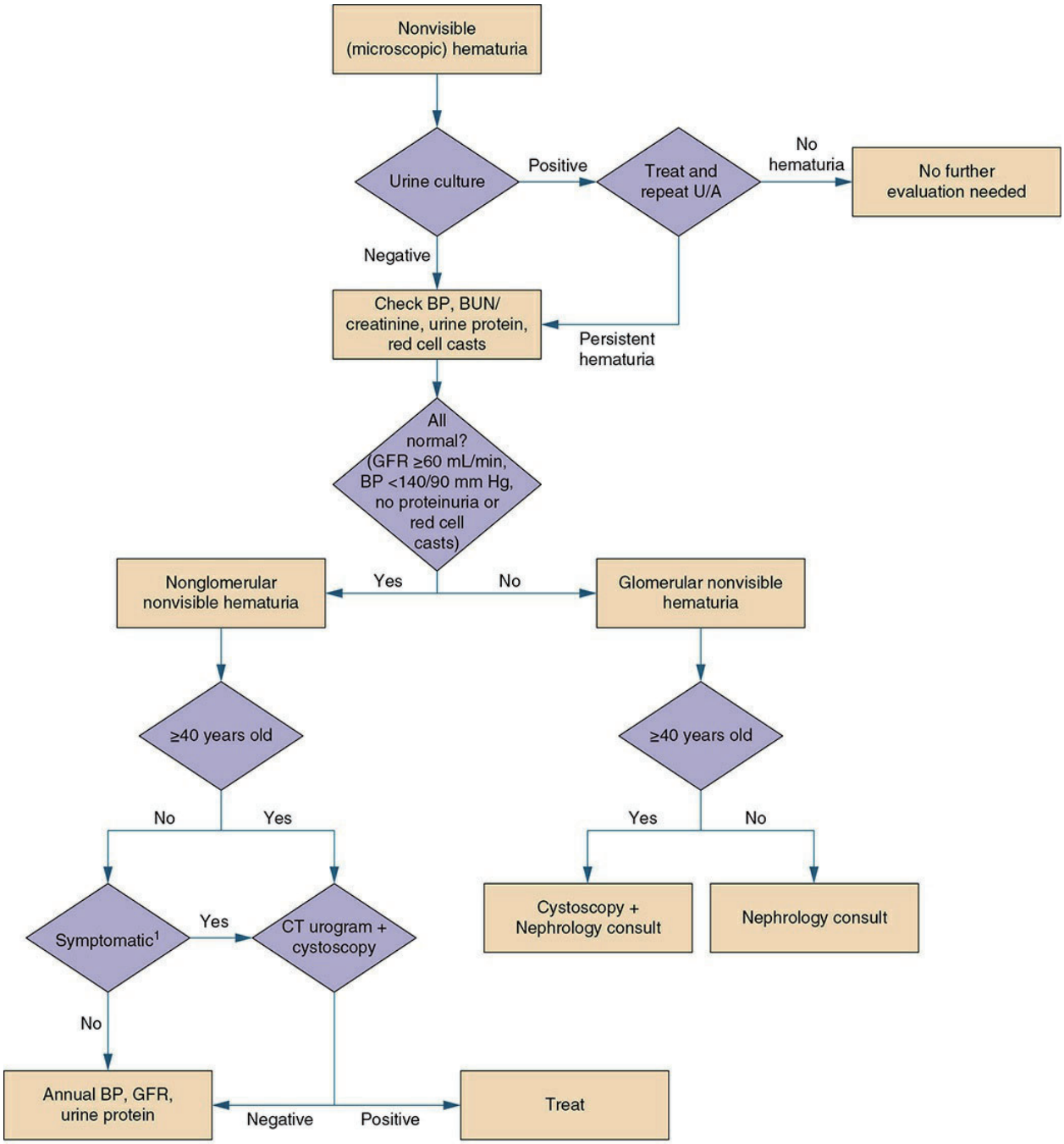
a. Benign prostatic hypertrophy (BPH)

b. Prostate cancer

c. Post prostatic procedure

d. Prostatitis

Figures 21-1 and 21-2 reorganize the differential diagnosis using pivotal points and outline the diagnostic approach to hematuria.



[1]Symptoms include dysuria, flank pain, abdominal pain, difficulty voiding.

BP, blood pressure; BUN, blood urea nitrogen; GFR, glomerular filtration rate; U/A, urinalysis.

Figure 21-1. Diagnostic approach to nonvisible (microscopic) hematuria.

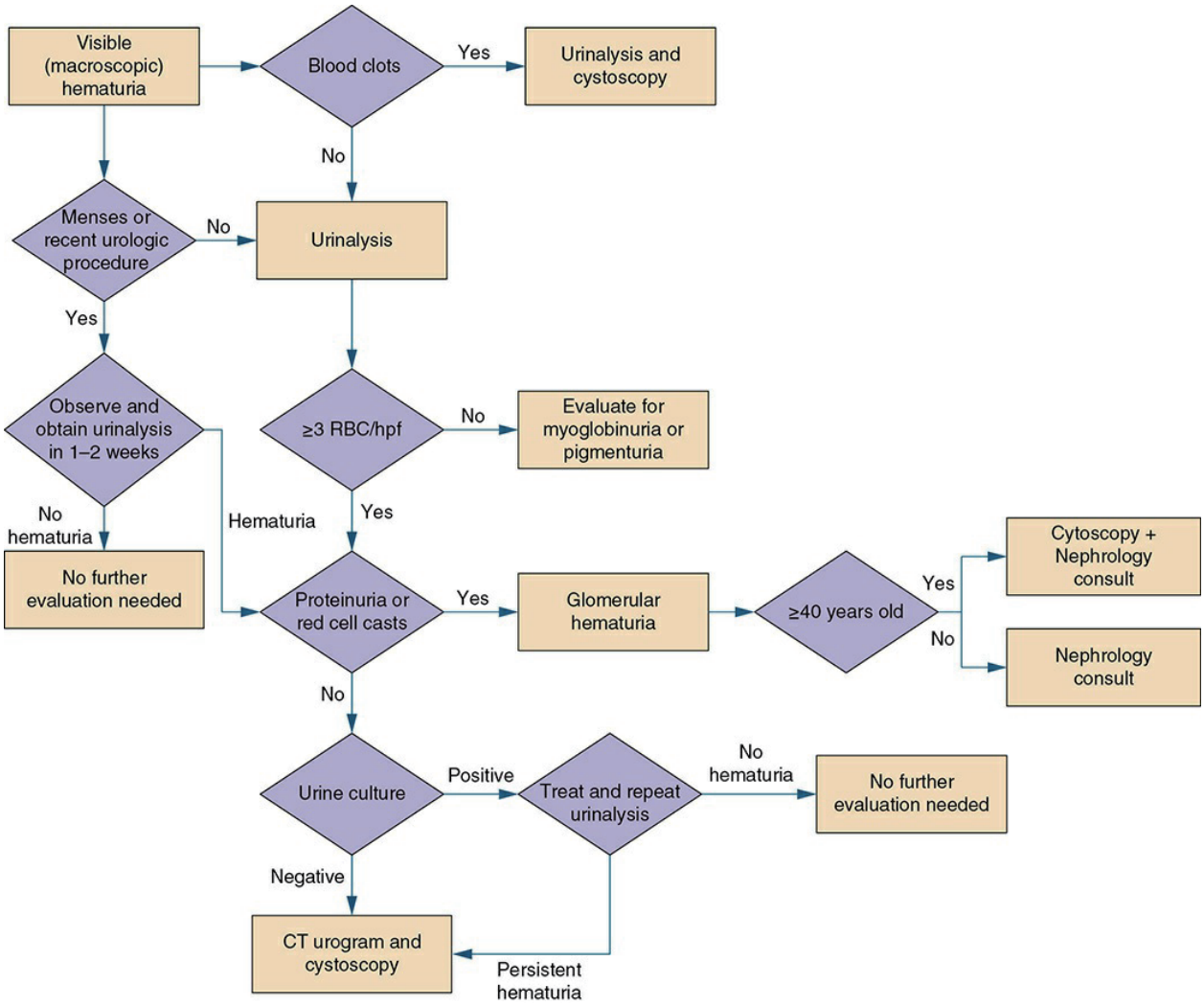


Figure 21-2. Diagnostic approach to visible (gross) hematuria.

1

Mr. A reports several episodes of painless visible (gross) hematuria over the last several days, along with occasional mild lower abdominal discomfort. He is feeling well otherwise and has no other complaints. His medical history is significant for chronic kidney disease (CKD) stage 3, hypertension treated with hydrochlorothiazide and enalapril, and a remote appendectomy. He has no family history of kidney stones, but his father did have prostate cancer diagnosed at age 77. Mr. A has smoked 1 pack of cigarettes per day for 35 years. He is a philosophy professor, and has no other known toxin exposures. Initial urinalysis shows many nondysmorphic RBCs, with no WBCs, bacteria, casts, or proteinuria.

At this point, what is the leading hypothesis, what are the active alternatives, and is there

a must not miss diagnosis? Given this differential diagnosis, what tests should be ordered?

RANKING THE DIFFERENTIAL DIAGNOSIS

Mr. A does not have the pivotal urinalysis findings that suggest a glomerular source of the hematuria. Therefore, nonglomerular causes should be considered first. The patient's sex (male), age (> 40 years), and 35 pack year smoking history are all risk factors for malignancy, so bleeding from a urothelial bladder cancer needs to move to the top of the differential diagnosis. Although he does not have abdominal or flank pain suggestive of renal colic, stone disease is common and should be considered. Prostate cancer, BPH, and prostatitis are also common, and men with prostatitis may have vague abdominal discomfort, as Mr. A does. Renal cell carcinoma (RCC) is rare but must always be considered in a patient with hematuria. The otherwise bland urinalysis makes interstitial causes and UTI unlikely. He has no history of radiation or chemotherapy to suggest an associated cystitis. Table 21-2 lists the differential diagnosis.

Table 21-2. Diagnostic hypotheses for Mr. A.

Diagnostic Hypotheses	Demographics, Risk Factors, Symptoms and Signs	Important Tests
Leading Hypothesis		
Bladder cancer	Painless hematuria sometimes with blood clots Smoking history Male sex Toxin exposure Age over 40	Cystoscopy Urine cytology CT urogram
Active Alternatives—Most Common		
Stone disease	**Bladder:** hematuria, bladder pain	Noncontrast CT Cystoscopy
	Ureter or kidney: hematuria, flank/abdominal pain, renal colic	Noncontrast CT
Benign prostatic hypertrophy	Urgency frequency, nocturia, urge incontinence, stress incontinence, hesitancy, poor flow, straining, dysuria	Rectal exam
Prostatitis	Abdominal pain, recent/concurrent urinary tract infection, fever, chills, urinary retention, recent prostate biopsy	Rectal exam, urinalysis, urine culture
Active Alternatives—Must Not Miss		
Prostate cancer	Hematuria	Rectal exam Prostate-specific antigen
Renal cell carcinoma	Hematuria Flank pain Abdominal mass	CT scan

Mr. A’s physical exam is normal, with no abdominal masses or tenderness. External genitalia are normal, and digital rectal exam shows a symmetric, nontender prostate without nodules. Serum creatinine is 1.8 mg/dL, unchanged from previous values.

Urine culture is negative.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

Leading Hypothesis: Bladder Cancer

Textbook Presentation

Bladder cancer classically presents as painless visible (gross) hematuria in an older male smoker. However, episodes of gross hematuria may be intermittent, and thus asymptomatic nonvisible (microscopic) hematuria may be the only sign for some patients. If present, symptoms may include dysuria or obstructive symptoms.

Disease Highlights

A. Accounts for 90% of urothelial cancers

B. Visible painless hematuria, often intermittent, occurs in 85% of patients

C. Risk factors for bladder cancer

1. Male sex and white race: bladder cancer is 3–4 times more likely to develop in white males than black males or white females
2. Smoking: accounts for 60% of bladder cancers in males and 30% in females
3. Age > 40 years: median age at diagnosis is 70 years
4. Preexisting urothelial cancer (RCC, ureteral, prostate)
5. History of pelvic radiation
6. Chronic UTI
7. Schistosomiasis (in Africa and the Middle East)
8. Industrial chemical/toxin exposure
    - **a.** Kidneys filter and concentrate metabolic toxins into the urine which pool in the bladder, promoting oncogenesis
    - **b.** Accounts for about 20% of bladder cancers
    - **c.** 10- to 20-year latency period between exposure and disease
    - **d.** Compounds associated with bladder cancer include aromatic amines, aniline dyes, nitrates, nitrites, coal, and arsenic.
    - **e.** Occupations associated with a higher risk of bladder cancer include miners, bus drivers, rubber workers, motor mechanics, leather workers, blacksmiths, machine setters, hairdressers, and mechanics.

D. Prognosis: 10-year survival for muscle-invasive cancer still confined to the bladder is 65–72%.

Evidence-Based Diagnosis

A. The diagnostic approach is based on the estimated pretest probability of disease.

B. Prevalence of cancer in patients with hematuria

1. Microscopic hematuria
    - **a.** Up to 8.9% of patients had a malignancy in 1 series
    - **b.** Another cohort found bladder cancer in 3.7%, RCC in 1%, and ureteral cancer in 0.2%.

c. Malignancy was extremely rare in patients under the age of 40 with microscopic hematuria.

2. Gross hematuria: studies generally included older patients who presented to "hematuria clinics"
   - **a.** Consistently > 10% had a malignancy and in some studies, the prevalence was > 25%
   - **b.** 20–25% had bladder cancer
   - **c.** 1.3–10% had prostate cancer
   - **d.** 0.6–2% had RCC
   - **e.** 21% had stones
   - **f.** 12–13% had BPH

Urothelial cancer is a must not miss diagnosis in patients with gross hematuria not due to an infection.

C. White light flexible cystoscopy with biopsies is the gold standard for diagnosing bladder cancer; random biopsies of bladder tissue are taken to detect carcinoma in situ not visible to the naked eye.

D. Hexaminolevulinate fluorescence cystoscopy is also useful for detecting carcinoma in situ.

E. Multiphasic CT urography is done with and without contrast and includes imaging in the excretory phase.

1. Has largely replaced other imaging modalities, such as IV pyelogram, ultrasonography, conventional CT, and retrograde pyelography to evaluate unexplained hematuria
2. Comparatively higher sensitivity (92–100%) and specificity (94–97%) for the detection of renal masses, urinary tract stones, and genitourinary transitional cell carcinomas
3. May improve the sensitivity of cystoscopy if done first
4. Delivers a relatively high radiation dose; therefore, some guidelines recommend avoiding in low-risk patients

F. Ultrasound

1. The sensitivity of ultrasound for bladder cancer is 63% and the specificity 99%.
2. Ultrasound is less sensitive than CT for detecting renal tumors < 3 cm.

G. Urine cytology and biomarkers

1. None of the many urine biomarkers investigated has adequate test characteristics.
2. Urine cytology sensitivity is 7–17% for low-grade and 53–90% for high-grade cancers; specificity is 90–98%.

Patients aged 40 years or older, or with visible urinary blood clots, require cystoscopy even if the bleeding is glomerular.

Treatment

A. Superficial or minimally invasive bladder tumors are treated with transurethral resection for both diagnostic confirmation and cure.

B. Intravesicular chemotherapy (most often with Bacillus Calmette-Guérin [BCG]) is given immediately after the operation.

C. Muscle-invasive tumors are treated with radical cystectomy and cisplatin-based chemotherapy.

MAKING A DIAGNOSIS

Although you are concerned about malignancy, because of his CKD you order an ultrasound rather than a CT scan. It shows a 1 mm stone in the right renal pelvis, and a 2 cm cyst in the left kidney. You order a PSA and refer him to urology for a cystoscopy.

Have you crossed a diagnostic threshold for the leading hypothesis, bladder cancer? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Alternative Diagnosis: Nephrolithiasis

See Chapter 3, Abdominal Pain.

Alternative Diagnosis: Prostate Cancer

See Chapter 2, Screening & Health Maintenance.

Alternative Diagnosis: BPH

See Chapter 28, Acute Kidney Injury.

Alternative Diagnosis: Prostatitis

See Chapter 16, Dysuria.

Alternative Diagnosis: Renal Cell Carcinoma

Textbook Presentation

RCC classically presents with the triad of hematuria, flank pain, and a palpable abdominal mass but now is far more commonly detected incidentally as a renal mass seen on a radiographic examination done for other reasons.

Disease Highlights

A. Epidemiology

1. Arises from the renal epithelium and accounts for over 80% of renal cancers, with a 1.6:1 male predominance and peak incidence between the sixth and eighth decades of life
2. About 2% of cases are associated with inherited syndromes like von Hippel-Lindau disease
3. Risk factors
    - **a.** Smoking
    - **b.** Obesity
    - **c.** Hypertension
    - **d.** Toxic exposures
    - **e.** Acquired cystic kidney disease associated with end-stage renal disease (ESRD)

B. Etiology

1. The most common histologic form is clear cell, which accounts for 75–85% of cases.
2. Other histologies are papillary (10–15%) and chromophobe (5–10%).
3. The pathogenesis is incompletely understood, but the von Hippel-Lindau (*VHL*) tumor suppressor gene is mutated in most sporadic cases of RCC.

C. Presentation

1. Many patients with RCC are asymptomatic until the disease is advanced, with roughly 25% having distant metastases or locally advanced disease at the time of presentation.
2. Hematuria occurs with tumor invasion of the renal collecting system, ranging from microscopic to visible blood clots.
3. An abdominal or flank mass, generally only palpable in thin individuals, is usually firm, homogenous, and nontender, moving with respiration.
4. Nonspecific symptoms, such as fatigue, weight loss, and anemia, are common.

D. Prognosis

1. Stage I: 5-year survival > 90%
2. Stage II: 5-year survival of 75–95%
3. Stage III who undergo nephrectomy: 5-year survival rate of 59–70%
4. Stage IV: median survival of 16–20 months; < 10% 5-year survival rate for patients with distant metastases

Evidence-Based Diagnosis

A. RCC appears as a solid renal lesion on abdominal imaging.

1. On ultrasound, the mass does not meet criteria for a simple cyst.
2. On CT, features of RCC include thickened irregular walls or septa and enhancement with IV contrast.

B. RCC can remain localized, invade surrounding fascia and adjacent organs, and/or metastasize.

1. CT scan is used for staging.
   - **a.** 78% sensitive and 96% specific for the detection of renal vein invasion
   - **b.** 83% sensitive and 88% specific for the detection of metastatic adenopathy
   - **c.** 46% sensitive and 98% specific for the detection of perinephric invasion
   - **d.** 100% specific for detecting adjacent organ invasion
2. Bone scan, CT chest, MRI, or PET scanning are used to detect distant metastases.

Treatment

A. For patients with isolated, solid renal masses, resection with either partial or complete nephrectomy is preferred to biopsy since it is both diagnostic and therapeutic; consultation with urology is essential to determine whether surgery or surveillance is indicated.

B. Deciding whether to perform a partial or complete (radical) nephrectomy depends on

1. Stage and location of the tumor
2. Baseline kidney function
3. Functional status
4. Presence of other comorbidities

C. A reasonable alternative for individuals at high risk for complications from surgery is thermal ablation (eg, cryotherapy or radiofrequency ablation).

D. Consultation with oncology is indicated for patients with locally advanced or metastatic RCC.

CASE RESOLUTION

Mr. A's cystoscopy detects a small papillary tumor localized to the uroepithelium of his bladder. Hexaminolevulinate fluorescence cystoscopy does not detect any carcinomas in situ. CT urography does not demonstrate any masses elsewhere in the upper urinary tract or kidneys. His bladder cancer is classified as superficial and he is treated with transurethral resection followed by BCG therapy. At a follow-up visit 1 year later he is cancer free and feeling well.

CHIEF COMPLAINT

Mr. S is a 24-year-old white man who comes to your office after being told there was ‘some blood detected’ on a screening urinalysis obtained 2 weeks ago during an Army enlistment physical. He has not seen any blood in his urine, is anxious to start basic training, and “doesn’t understand what all the fuss is about.” He denies any dysuria, abdominal pain, fevers, or urethral discharge. Exam is notable for a fit, well-developed young man in no acute distress. His vital signs were temperature, 37.2°C; pulse, 68 bpm; BP, 126/78 mm Hg; RR, 16 breaths per minute. His exam is completely normal with a notable absence of abdominal pain, costovertebral angle tenderness, urethral discharge or testicular pain, and lower extremity edema.

His screening and in-office urinalyses both show 2+ protein, 2+ blood, and 5–10 RBCs/hpf. The dipstick is otherwise negative, and there are no WBCs or bacteria. Microscopic analysis of the urine in the office also reveals occasional dysmorphic RBCs but no RBC casts.

At this point, what is the leading hypothesis, what are the active alternatives, and is there a must not miss diagnosis? Given this differential diagnosis, what tests should be ordered?

RANKING THE DIFFERENTIAL DIAGNOSIS

Mr. S is asymptomatic with nonvisible (or microscopic) hematuria. Based on the 2 separate urinalyses, it is persistent. In patients younger than 40 without risk factors, cancer is an uncommon cause of asymptomatic nonvisible hematuria; in the absence of lower urinary symptoms, a urologic cause is rare. Notably, the concomitant proteinuria and the dysmorphic RBCs are pivotal points for a glomerular source. The most common glomerular causes are IgA nephropathy and TBMN. Table 21-3 lists the differential diagnosis.

Table 21-3. Diagnostic hypotheses for Mr. S.

Diagnostic Hypotheses	Demographics, Risk Factors, Symptoms and Signs	Important Tests
Leading Hypothesis		
IgA nephropathy	Episodes of gross hematuria (tea-colored urine) that coincide with respiratory infections	Urinalysis with microscopy Serum creatinine Renal biopsy
Active Alternative		
Thin basement membrane nephropathy	Family history of hematuria without history of chronic kidney disease	Urinalysis with microscopy Serum creatinine Renal biopsy
Active Alternative		
Infection-related glomerulonephritis	Antecedent group A streptococcal pharyngitis 1–3 weeks prior to episode of gross hematuria, often with high BP and edema	Urinalysis with microscopy Serum creatinine Antibodies to streptococcal antigens Serum complement levels
Other Alternative		
Alport syndrome	Hematuria with strong family history of progressive renal disease and sensorineural hearing loss	Urinalysis with microscopy Serum creatinine Family history Renal biopsy

The patient reports no prior medical or surgical history; he has not seen a physician since his last pediatrician visit at age 18. No one in his family has any known history of hematuria or kidney problems. He has been in a stable, monogamous relationship with his girlfriend for over a year and is not taking any medications or supplements. On more detailed questioning, he does recall “3 or 4” previous episodes of his urine changing color for a few days, which he associated with colds or minor respiratory infections. Basic metabolic profile is normal, with a creatinine of 0.9 mg/dL and BUN of 12 mg/dL.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

Leading Hypothesis: IgA Nephropathy

Textbook Presentation

IgA nephropathy (IgAN) most commonly presents with visible hematuria within 12–72 hours of a mucosal (typically an upper respiratory) infection. It can also be discovered upon detection of asymptomatic, nonvisible hematuria with or without proteinuria during routine medical screening.

Disease Highlights

A. The most common cause of primary glomerulonephritis worldwide.

1. Peak incidence of IgAN is between the second and fourth decades of life, though it can present at any age.
2. Occurs with greatest frequency in Asians and whites.

B. An important cause of progressive CKD, with ESRD developing in up to 50% of patients within 25 years of diagnosis.

C. Etiology of IgAN

1. Caused by glomerular deposition of A1 isotype of IgA in the mesangium.
2. No evidence of a role for any specific antigen despite the relation between mucosal infections and episodes of visible hematuria.
3. Most cases of IgAN are sporadic, although familial cases do occur and appear to be transmitted as an autosomal dominant trait with incomplete penetrance.

D. Clinical manifestations of IgAN

1. One or more episodes of visible hematuria, usually associated with upper respiratory infection (often called **synpharyngitic hematuria**) and sometimes accompanied by flank pain and low-grade fever (present in 40–50% of patients).
2. Nonvisible hematuria and typically mild proteinuria, detected incidentally on routine screening (present in 30–40% of patients).
3. Advanced, progressive CKD, hypertension, and heavy proteinuria, in addition to hematuria (seen in small proportion of patients); nephrotic range proteinuria (present in ~5% of patients)
4. IgAN rarely occurs secondary to other conditions like cirrhosis, celiac disease, and HIV infection, all of which are associated with a high frequency of IgA deposition.

Evidence-Based Diagnosis

A. Urine dipstick with microscopy and culture should be used to rule out infection, confirm the findings of hematuria, and evaluate for proteinuria.

B. A definitive diagnosis can only be made by renal biopsy with immunofluorescence or immunoperoxidase studies for IgA deposits.

1. In the absence of proteinuria, hypertension, or decreased glomerular filtration rate (GFR), the clinical course (at least short-term) of patients with IgAN is generally benign and kidney biopsy is usually not indicated; periodic monitoring is recommended in these cases.

2. Proteinuria (> 500–1000 mg/day), elevated serum creatinine, or hypertension suggests more severe or progressive disease and are indications for kidney biopsy to establish the diagnosis.

C. The pathognomonic biopsy finding of IgAN is prominent, globular deposits of IgA in the mesangium on immunofluorescence microscopy.

Treatment

A. Patients with isolated hematuria, normal GFR, and no significant proteinuria should be monitored every 6–12 months for signs of progression (worsening proteinuria, BP, and GFR).

B. Clinical predictors of progression of IgAN, including proteinuria > 500–1000 mg/day, decreased GFR, and hypertension often signal the need for treatment.

C. Treatment is primarily aimed at reducing proteinuria and optimizing BP to minimize risk of progression.

D. Treatment of progressive IgAN

1. Angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) therapy slows progression by optimizing BP control and reducing proteinuria.
2. Fish oil has also been used in IgAN patients with > 1000 mg/day of proteinuria despite 3–6 months of ACE inhibitor or ARB therapy, although a benefit has not been clearly established.
3. Some patients with IgAN with signs of more severe inflammatory disease on biopsy may require immunosuppressive therapy.
4. Kidney transplantation is an option for patients with IgAN who have had progression to ESRD, but recurrence is common.

MAKING A DIAGNOSIS

A spot urine total protein to creatinine ratio, to quantify the amount of protein in the urine, is found to be 1100 mg/day. He now remembers that he did have a sore throat prior to the first urine sample.

Have you crossed a diagnostic threshold for the leading hypothesis, IgA nephropathy? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Alternative Diagnosis: Thin Basement Membrane Nephropathy

Textbook Presentation

Most individuals with TBMN have isolated hematuria with normal kidney function, no or minimal proteinuria, and a uniformly thinned glomerular basement membrane (GBM) on electron microscopy analysis of biopsy specimen.

Disease Highlights

A. The most common cause of persistent hematuria in children and adults

1. Occurs in at least 1% of the general population and is often familial
2. A family history of hematuria is present in 30–50% of TBMN cases.

B. Characteristically presents with persistent or intermittent hematuria incidentally discovered on routine urinalysis

1. Most patients have isolated hematuria, which can present at virtually any age, without proteinuria or kidney impairment.
2. Dysmorphic RBCs are commonly seen, and RBC casts may occur.
3. Episodes of visible hematuria may occur in a small percentage of individuals with TBMN (12%) but are far more common in Alport syndrome (33%) and IgA nephropathy (88%).
4. Proteinuria is rarely seen in children with TBMN, but mild proteinuria (up to 1 g/day) may be seen in a minority of adult patients.

C. TBMN is caused by defects in type IV collagen genes, which leads to a diffuse thinning of the GBM seen on electron microscopy.

D. The long-term prognosis in most patients with true TBMN is excellent.

Evidence-Based Diagnosis

A. The only way to definitively diagnose TBMN is by kidney biopsy and electron microscopy.

1. Kidney biopsy is usually not performed in patients with isolated hematuria, normal kidney function, and no or minimal proteinuria. The diagnosis is often inferred in these patients with positive family history of hematuria and negative family history of CKD.
2. Kidney biopsy is more commonly performed in patients with suspected TBMN who also have proteinuria (> 200–300 mg/day).

B. Biopsy reveals diffuse, uniform thinning of the GBM on electron microscopy, and the absence of other significant glomerular pathology.

C. Immunohistochemical evaluation of the type IV collagen alpha-3 to alpha-5 chains is useful in helping distinguish between TBMN and early Alport syndrome (with microscopic hematuria and thin GBM), as these chains are usually absent or abnormally distributed in Alport syndrome.

Treatment

A. Progressive CKD with TBMN is rare, but regular follow-up and monitoring is important.

B. While there are no proven therapies for TBMN, a goal BP of < 130/80 mm Hg and angiotensin inhibition is recommended for patients with TBMN and proteinuria > 1 g/day.

Alternative Diagnosis: Infection-Related Glomerulonephritis

Textbook Presentation

The classic presentation of infection-related glomerulonephritis (IRGN) is new onset of hematuria, proteinuria, and edema, often with hypertension and mild acute kidney injury, following or concurrent with an infection.

Disease Highlights

A. Epidemiology

1. In the developing world, IRGN (especially poststreptococcal glomerulonephritis [GN]) occurs primarily in children (ages 6–10) and young adults, with a male predominance (2–3:1).
2. In the developed world, IRGN affects mostly adults, especially those with immunocompromising comorbidities such as diabetes mellitus and alcoholism.

B. Etiology

1. Upper respiratory and skin infections are the 2 most common sites of infection leading to IRGN, although multiple other sites have also been implicated.
2. Historically, most cases have been attributed to group A streptococci, specifically *Streptococcus pyogenes.*
3. More recently, it has become clear that other strains of streptococci (groups C and G), staphylococci, gram-negative bacilli, mycobacteria, parasites, fungi, and viruses can also cause IRGN.
4. One-third to one-half of cases of IRGN in developed countries are associated with infections of gram-negative bacilli.

C. Clinical manifestations

1. Acute nephritic syndrome (poststreptococcal GN is the prototypical form)
   - **a.** Presents with hematuria, proteinuria, and edema, often accompanied by hypertension and mild acute kidney injury
   - **b.** Urinary output usually improves after 5–7 days, followed rapidly by resolution of edema and normalization of BP
2. Rapidly progressive nephritic syndrome
   - **a.** Rarely, acute postinfectious GN (usually poststreptococcal) is complicated by rapidly worsening GFR
   - **b.** Crescent formation is often present on biopsy but tends to be limited.
3. Subclinical or asymptomatic GN
   - **a.** Present in many patients with mild, self-limited streptococcal infections
   - **b.** Characterized by low-grade proteinuria (< 1 g/day), pyuria, and nonvisible (microscopic) hematuria; often goes undetected

Evidence-Based Diagnosis

A. In children, nephritis typically follows pharyngitis by 1–2 weeks and skin infection by 2–4

weeks.

1. During this time, asymptomatic nonvisible (microscopic) hematuria and proteinuria is often present.
2. Upon symptomatic presentation (eyelid and diffuse edema, smoky colored urine), a urinalysis shows proteinuria (mild to nephrotic range), pyuria (97%), and often hematuria (30–37%) with RBC casts.
3. Acute kidney injury and hypertension are also common (60–80%).
4. Hypocomplementemia is present in 90% of children with poststreptococcal GN and 35–80% of adults with IRGN.
   a. C3 is typically low while C4 is normal.
   b. One-third of patients with IRGN will have both low C3 and low C4.
5. Serologies for recent streptococcal infection (ASO, DNase B, streptokinase, hyaluronidase, anti-NAD) are often positive, even when patients do not report recent respiratory or skin infection.
   a. The streptozyme test measures all 5 of these streptococcal antibodies and performs better than any individual antibody measurement alone.
   b. It has a sensitivity of 95% in patients with recent group A streptococcal pharyngitis and 80% in those with streptococcal skin infections.
6. Biopsy is usually not recommended in children.

B. In a significant proportion (45%) of adults, the precipitating infection is still present and only discovered at the time IRGN is diagnosed.

1. Adults present with gross hematuria and diffuse edema; proteinuria can lead to foamy urine and hypertension can cause headaches.
2. Exam may reveal signs of infection, such as pharyngitis, pneumonia, cellulitis/abscess, endocarditis, or urethral/vaginal discharge.
3. Older adults (25%) may have additional signs of volume overload (increased jugular venous pressure, S_3 gallop, pulmonary crackles, lower extremity edema) stemming from acute volume overload precipitated by the acute kidney injury.
4. Urinalysis shows at least nonvisible (microscopic) hematuria, although gross hematuria is often already present.
5. Proteinuria (mild to nephrotic range) is usually present, and RBC casts may be seen on microscopy.
6. Biopsy is usually recommended in adults to confirm diagnosis and rule out glomerulonephritides that require immediate immunosuppressive therapy.

Treatment

A. Children should be treated with supportive therapy.

B. Adults

1. Treat underlying infection, which is often ongoing at the time of diagnosis.
2. Manage complications of nephritis.

a. Antihypertensives, specifically ACE inhibitor if moderate to heavy proteinuria

b. Diuretics and sodium restriction

3. Immunosuppressive therapy is not recommended.

C. Prognosis

1. Complete recovery occurs in almost all children, although potentially with increased likelihood of CKD and hypertension later in life.
2. Adults with IRGN have a poorer prognosis.

a. Up to 50% have persistent kidney dysfunction, and up to 33% progress to ESRD.

b. Elderly and diabetic patients have the highest risk of persistent CKD and ESRD.

CASE RESOLUTION

In the absence of any family history of hematuria or CKD, IgA nephropathy is the most likely diagnosis. Mr. S has normal BP and kidney function but needs a biopsy because of the proteinuria. The results show classic IgA nephropathy. Given his significant proteinuria, which is a risk factor for more rapid decline in kidney function, Mr. S was started on an ACE inhibitor with close BP monitoring for a target < 125/75 mm Hg. After 1 month, repeat testing demonstrated persistent nonvisible hematuria, stable kidney function, and that the proteinuria had decreased to 250 mg/day. Although he was disqualified from military service, he continued with regular follow-up every 6–12 months and has done well without significant progression of his disease.

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